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Potent, Novel in Vitro Inhibitors of the *Pseudomonas aeruginosa* Deacetylase LpxC

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Deacetylation of uridyldiphospho-3-*O*-(*R*-hydroxydecanoyl)-*N*-acetylglucosamine by LpxC is the first committed step in the *Pseudomonas aeruginosa* biosynthetic pathway to lipid A; homologous enzymes are found widely among Gram-negative bacteria. As an essential enzyme for which no inhibitors have yet been reported, the *P. aeruginosa* LpxC represents a highly attractive target for a novel antibacterial drug. We synthesized several focused small-molecule libraries, each composed of a variable aromatic ring, one of four heterocyclic/spacer moieties, and a hydroxamic acid and evaluated the LpxC inhibition of these compounds against purified *P. aeruginosa* enzyme. To ensure that the in vitro assay would be as physiologically relevant as possible, we synthesized a tritiated form of the specific *P. aeruginosa* glycolipid substrate and measured directly the enzymatically released acetate. Several of our novel compounds, predominantly those having fluorinated substituents on the aromatic ring and an oxazoline as the heterocyclic moiety, demonstrated in vitro IC_{50} values less than 1 μM. We now report the synthesis and in vitro evaluation of these *P. aeruginosa* LpxC inhibitors.

Introduction

Emerging bacterial resistance to current antibiotic drugs has driven the search for novel prokaryotic targets and for novel molecules to inhibit the activity of these targets. The lipid A biosynthetic pathway, which is both unique and essential to Gram-negative bacteria, presents several good candidate enzymes.[1] LpxC, which catalyzes the first committed step in the lipid A pathway (Figure 1) is an essential enzyme[2] with homologues in more than 40 Gram-negative species. While there is no mammalian homologue of LpxC, the fact that it is a Zn-dependent amidase[3] places it in a class of enzymes for which inhibitors have been described.[4]

Merck scientists had previously discovered that aryl-oxazoline hydroxamic acids were inhibitors of this enzyme and reported that L-161,240 was a potent inhibitor of the LpxC from *Escherichia coli*; this compound also inhibited growth of *E. coli*.[5] However, this compound had no effect on the growth of another pathogenic Gram-negative species, *Pseudomonas aeruginosa*, and in vitro activity toward *P. aeruginosa* LpxC was 50- to 100-fold weaker than toward the *E. coli* enzyme.[6] We initiated a discovery project targeting the *P. aeruginosa* LpxC by synthesizing novel compounds of the general motif shown in Figure 2 in which the Zn-binding hydroxamic acid was conserved and the aryl and heterocyclic moieties were varied. We particularly focused on the role of hydrophobic substituents and aromatic heterocycles in the aromatic moiety. The acylserine analogues of selected oxazolines were also synthesized for screening.

Because *P. aeruginos*a was the target organism, we required a sensitive in vitro assay specific for the *P. aeruginosa* LpxC. To achieve this, we prepared the native *P. aeruginosa* substrate with a tritiated *N*-acetyl group and assayed the enzymatically released tritium directly. We now describe the synthesis of three heterocyclic classes of inhibitors (oxazolines, thiazolines, and oxazines), the development of a radioligand assay for *P. aeruginosa* LpxC, and the evaluation of these compounds in our assay.

Results

Chemistry. Oxazolines and Acylserines. One modification that may increase hydrophobicity with minimal steric perturbation is the replacement of hydrogens with fluorines. Compounds **35** and **5** were synthesized as direct analogues of the best reported *E. coli* inhibitors of this class shown in Figure 2. Because the [*R*] stereochemistry at C-4 was reported to be significantly preferred,[3,5] we synthesized **35** and **5** from D-serine methyl ester using Burgess reagent at 80 °C and installed the hydroxamic acid by a stereospecific route[5b,7] as shown in Scheme 1.

We subsequently found that diethylaminosulfur trifluoride (DAST) at low temperatures gave consistently

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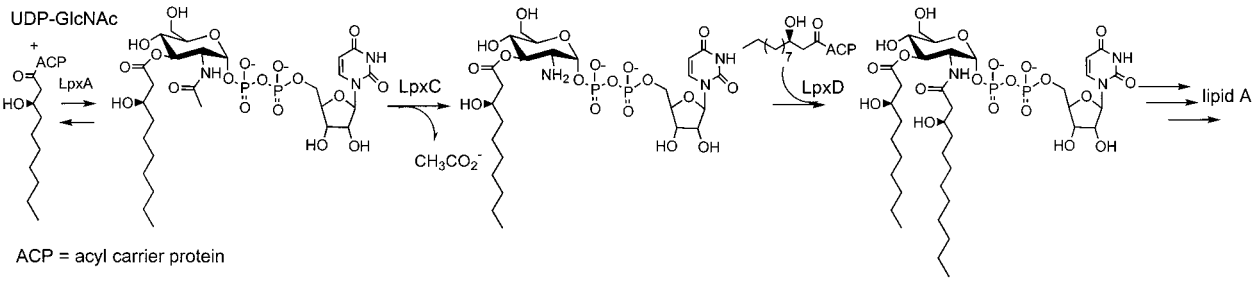


Figure 1. LpxC catalyzes the deacetylation of UDP-3-*O*-(*R*-3-hydroxydecanoyl)-GlcNAc to the corresponding glucosamine. This is the first committed step in the biosynthetic pathway to lipid A, an essential component of the Gram-negative outer membrane.

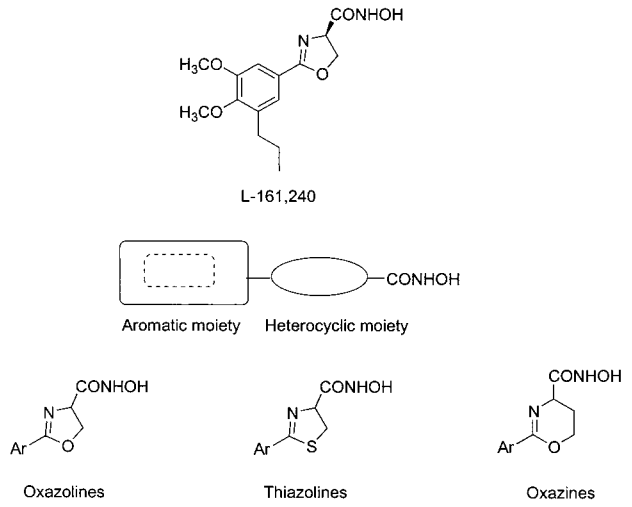
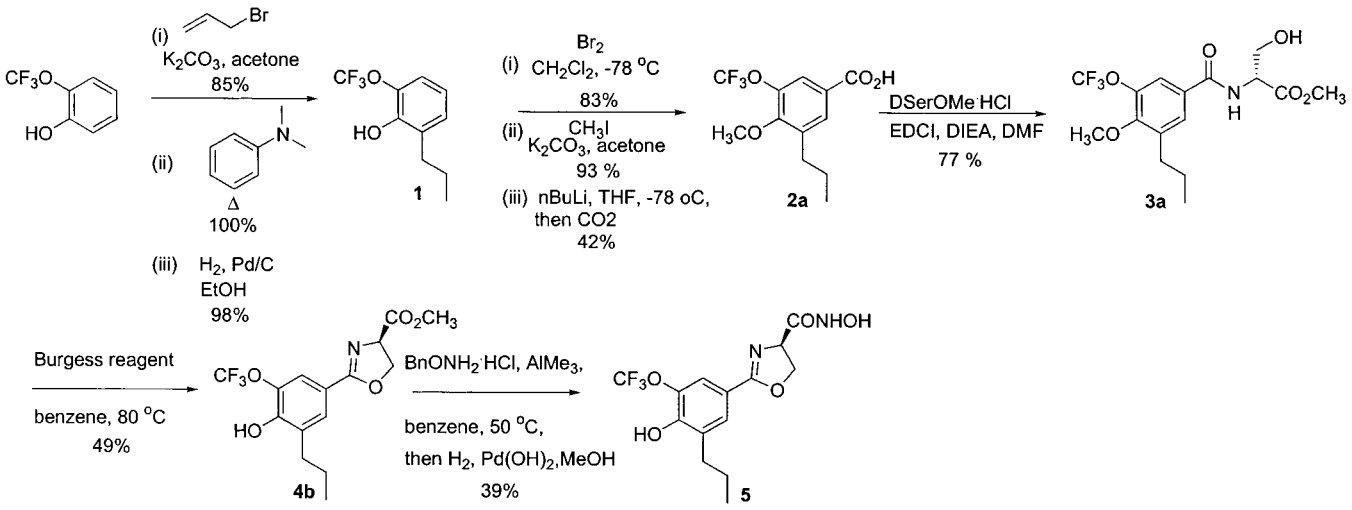


Figure 2. Libraries of LpxC inhibitors targeted against *P. aeruginosa* were designed by varying a set of aromatic rings fused to a set of heterocyclic five- and six-membered rings, all containing a hydroxamic acid as a Zn-binding group. A related series of compounds, exemplified by L-161,240, had been previously reported as inhibitors of the *E. coli* LpxC by researchers at Merck.

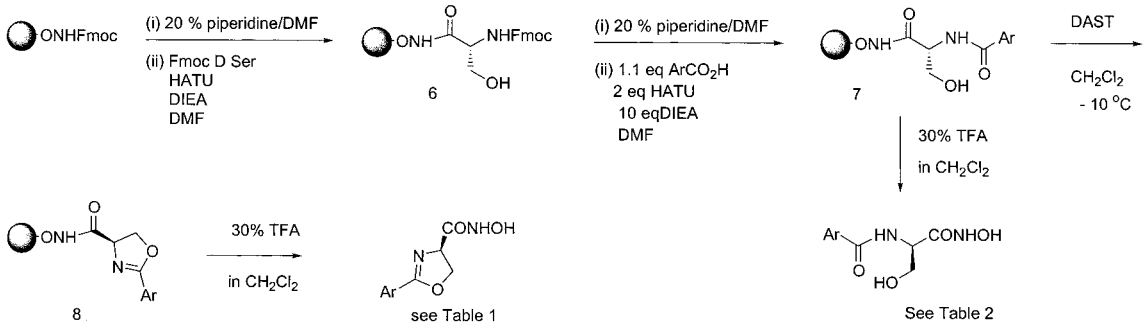
better results than Burgess reagent at higher temperatures, and DAST was used in all subsequent syntheses (Schemes 2 and 4). Initial efforts focused on solid-phase parallel synthesis (Scheme 2) for which the aromatic acids were generally commercially available. As our SAR developed, the more focused analogues required specific benzoic acids to address questions concerning the effects of functional group characteristics and placement on potency. The customized benzoic acids that were synthesized for conversion to the corresponding serine derivatives are shown in Scheme 3. Since early bioassay results indicated that aryl units bearing F, CF_3, and CF_3O groups had increased potency, these functions were the focus of the synthetic effort.

Although several solid-phase syntheses of hydroxamic acids have been reported,[8] the chemistry for solution-phase parallel synthesis (Scheme 4) that we developed gave consistently better results over a wide variety of analogues. The initial condensation of the aromatic acid with serine methyl ester was straightforward by any of the three methods used. The choice of hydroxamic acid installation (methods D−G) was dictated by the functionality of the precursor ester. The original method in Scheme 1 is designated as method D. Methods E and F were used with functional groups sensitive to hydrogenolysis; acid-labile anisyloxamines (method E) were the most amenable to parallel synthesis. Anisyloxyamine HCl, while commercially available in small quantities,[9] was prepared in multigram quantities in three steps from *p*-methoxybenzyl chloride (Scheme 4). Methoxide-promoted ester aminolysis with hydroxylamine (method F) afforded good yields and simplified purifications but led to partial racemization at the α carbon of the serine derivative (C-4 of the oxazolines). CD spectral determinations of the optical purities of selected products indicated % ee values of 80−95+% for acylserine hydroxamic acids and 30−87% for the oxazolines. Methods D, E, and G, which preserve the stereochemistry, were used in the analogues in which we wanted to establish optical purity. The general methods of Scheme 4 were

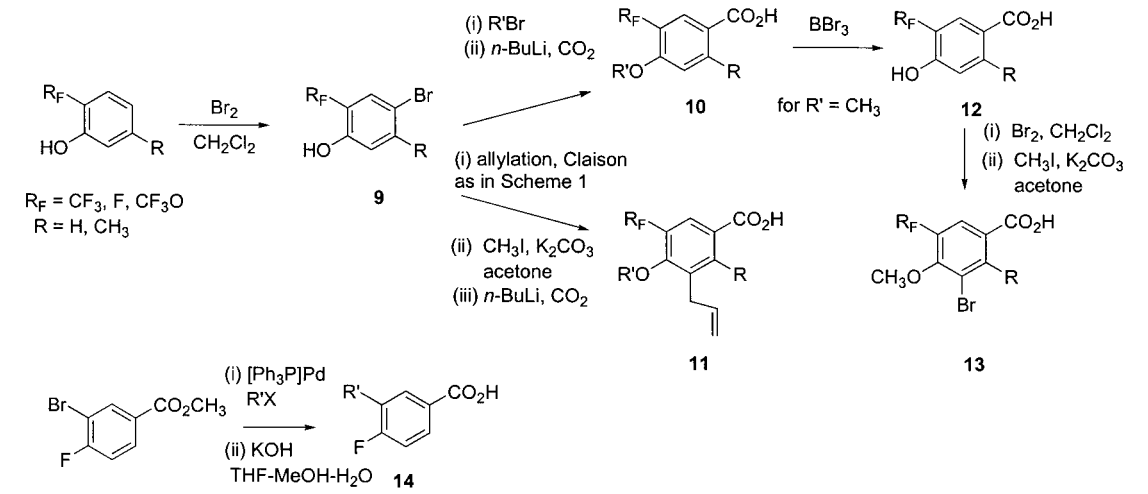
Scheme 1



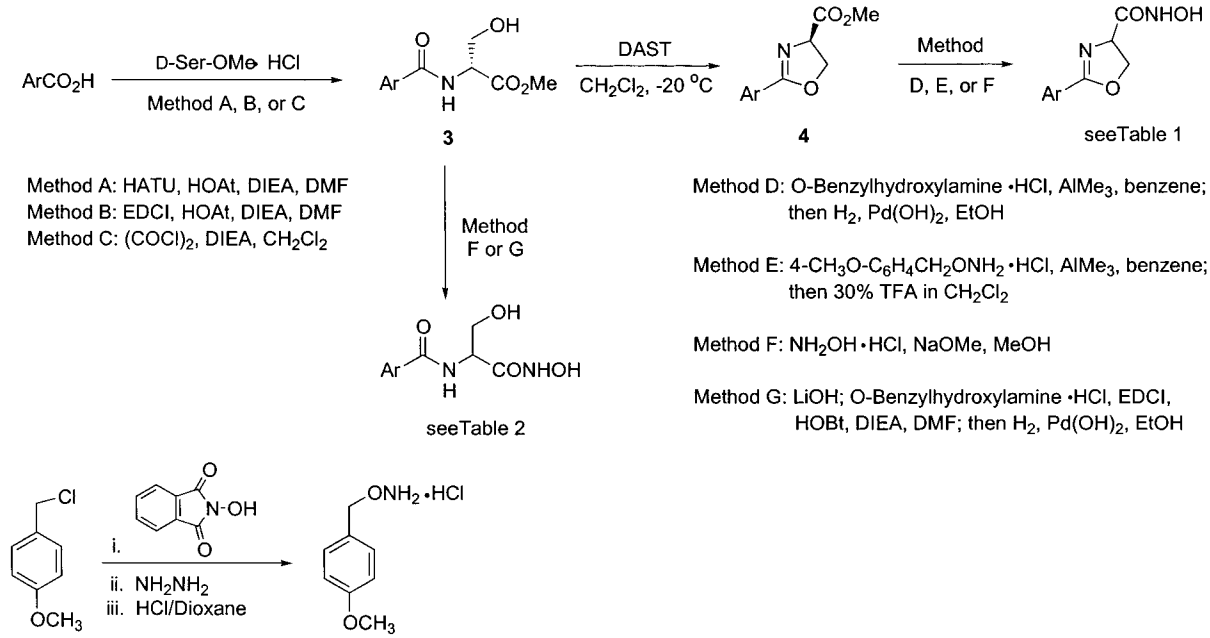
Scheme 2



Scheme 3



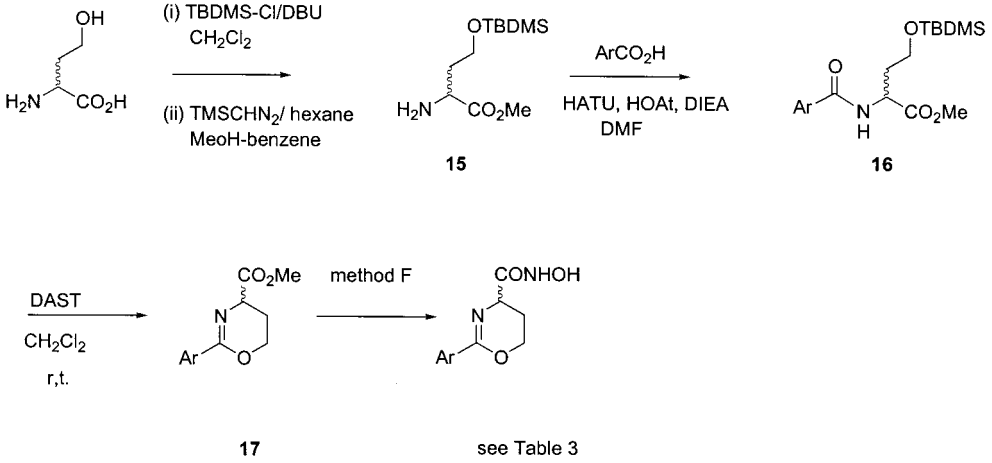
Scheme 4



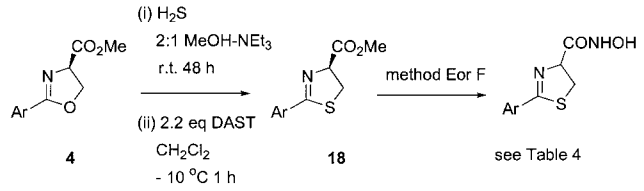
followed for all solution-phase syntheses and, in analogy to the diversion of intermediates **7** in Scheme 2, provided for the diversion of intermediates **3** to the *N*-aroylserine hydroxamic acids shown in Table 2.

Oxazines. Oxazines have been synthesized via the metal-catalyzed cyclization of *β*-amino alcohols with nitriles,[10] but we explored a novel and direct route (Scheme 5) that modified our oxazoline synthesis to accommodate homoserine as the starting material. Since for oxazines we had no precedent to follow for preferred stereochemistry, we used D,L-homoserine. The amino acid was sequentially protected as the methyl ester, *tert*-butyldimethylsilyl ether, then acylated with aromatic acids that had produced active oxazoline derivatives. Treatment with 6 equiv of DAST at ambient temperature for 12 h effected both O-desilylation and cyclization to the oxazine. The methyl ester was converted to the hydroxamic acid using method F.

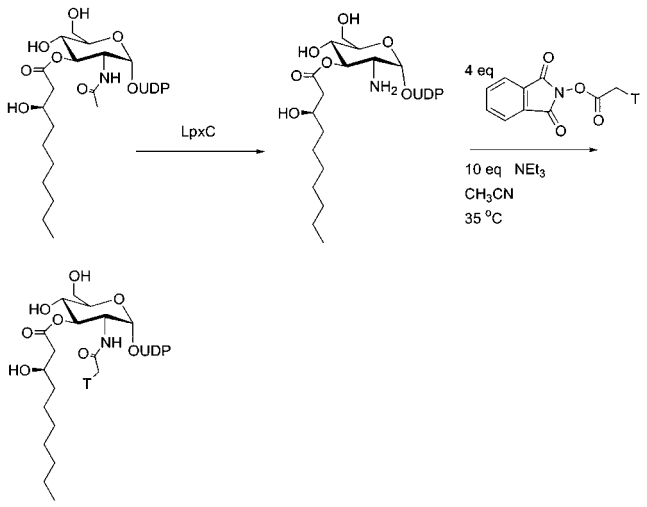
Scheme 5



Scheme 6



Scheme 7



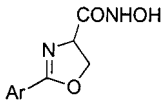
Thiazolines. Several routes to the thiazolines have been reported.[11] In our hands, the method of Wipf[12] (Scheme 6) gave both good yields and the efficiency of common oxazoline intermediates for both classes of compounds. The thiazoline methyl esters could be converted to the corresponding hydroxamic acids via either method E or F, but method F gave products needing minimal purification (typically trituration with cold methanol) and was therefore selected for our parallel synthesis.

Assay Development. Previously described assays for *E. coli* LpxC relied on chromatographic separation of deacetylated product,[1,3,6,13] or on the use of surrogate substrates.[14] While the predicted amino acid sequences of *P. aeruginosa* and *E. coli* LpxC share 82% similarity and 57% identity, the differences may account for their observed differences in their sensitivities to inhibitors.[15] Further, the native substrates for these enzymes differ: the LpxC substrate in *E. coli* is uridyldiphospho-3-*O*-(*R*-hydroxymyristoyl-*N*-acetylglucosamine (3-*O*-myristoyl UDPGlcNAc), but in *P. aeruginosa* it is 3-*O*-(*R*-3-hydroxydecanoyl) UDPGlcNAc. We employed a mixed chemoenzymatic strategy (Scheme 7)[1a,16] to prepare [^{3}H−CH_3CONH]−3-*O*-(*R*-3-hydroxydecanoyl) UDPGlcNAc at a specific activity of 14−17 Ci/mmol. A low level of the acyl migration (from O3 to O4 and then to O6 as described by Anderson et al.[1a]) occurred during the isolation of the tritiated substrate (see Experimental Section) but did not interfere with the assay. Control experiments with unlabeled substrate acyl migration products indicate that these were neither substrates nor inhibitors. The tritiated substrate was used in an assay that measured the cleaved [^{3}H]-acetate, adapted to a 96-well format from the procedure described by Hyland et al.[17] Incubation of the [^{3}H] substrate with *P. aeruginosa* LpxC (2 nM) at 22 °C for 90 min, followed by absorption with charcoal, left a supernatant that contained enzymatically released [^{3}H]-acetate, with a background as low as ≤200 cpm, thereby giving us both sensitivity and specificity. All compounds in Tables 1−4 were evaluated in this assay.

Discussion

Oxazolines. We explored diversity in the aromatic ring with emphasis on hydrophobic and heterocyclic functions. The modest potencies of the *p*-toluyl derivative **19** and the *p*-F derivative **35** indicated that even simple 2-aryloxazoline hydroxamic acids might be inhibitors of the *P. aeruginosa* LpxC enzyme (Table 1), with the *p*-F group being nearly 4-fold more active than the *p*-Me species. Consistent beneficial effects of fluorine-containing groups are demonstrated by the data in Table 1. The trifluoromethoxy group appears to be the best substituent and is optimally placed at the meta or para position. For enhanced activity, it is placed in the meta position and combined with an alkoxy group at the para position. The 3-trifluoromethoxy compounds do not appear to be highly sensitive to the nature of the 4-alkoxy group as long as this complementary group is present. Analogues **5** and **20**−**24** all display a similar improvement over **25**. Lone pair orientation may be one of the factors contributing to enzyme affinity. In the para-fluoro-substituted series, addition of alkyl or alkoxy at the meta position had a similar beneficial effect on the potency (**35** versus **36**−**38** and **44**, for example).

Table 1. Configuration and in Vitro *P. aeruginosa* LpxC Inhibition of 2-Aryloxazolines



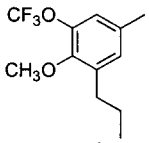
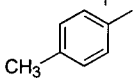
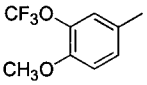
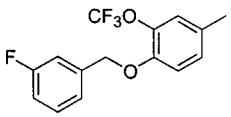
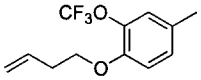
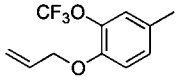
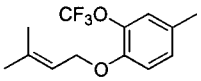
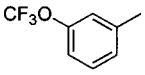
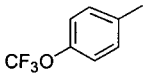
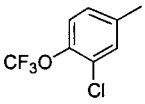
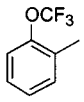
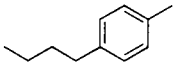
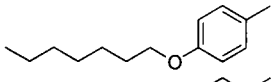
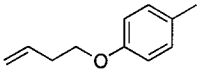
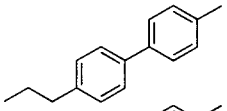
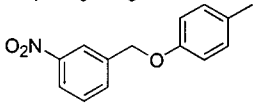
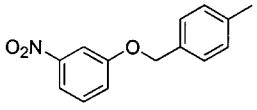
	Ar	Configuration %-ee R[a]	IC_{50} (μM)
5		>98%	0.5
19[b]		95+%	20
20		30%	0.16
21		40%	0.25
22		35%	0.35
23		racemic	0.12
24		racemic	0.19
25		95+%	6.0
26		95+%	5.0
27		>30%	30
28		95+%	>10
29		95+%	7.3
30		95+%	>30
31		95+%	5.6
32		95+%	0.28
33		>30%	1.0
34		>30%	0.56

Table 1 (Continued)

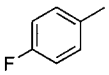
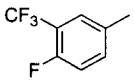
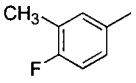
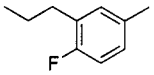
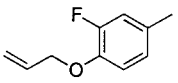
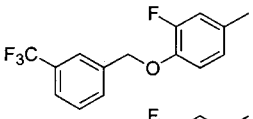
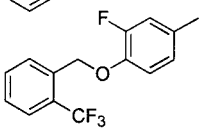
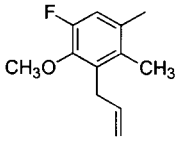
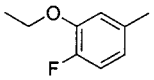
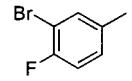
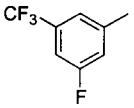
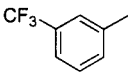
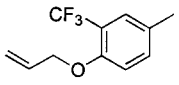
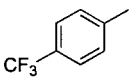
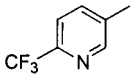
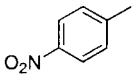
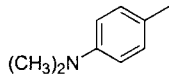
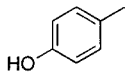
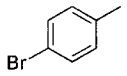
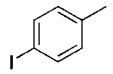
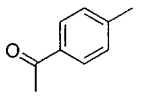
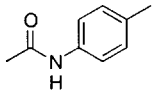
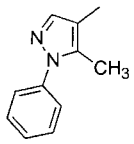
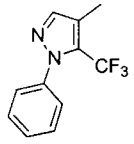
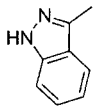
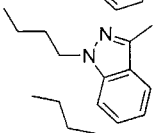
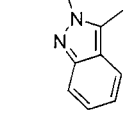
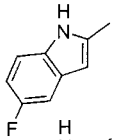
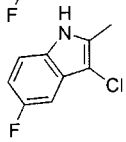
	Ar	Configuration %-ee R[a]	IC_{50} (μM)
35		>98%	6.0
36		>30%	1.3
37		65%	1.2
38		>98%	0.96
39		racemic	1.4
40		>30%	0.84
41		racemic	9.6
42		>30%	9.0
43		>30%	3.3
44		>30%	1.0
45		>30%	4.9
46		>30%	25
47		95+%	2.5
48		>30%	2.2
49		>20%	7.8
50		>30%	10

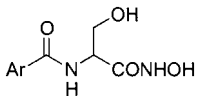
Table 1 (Continued)

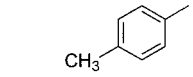
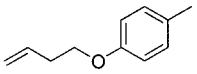
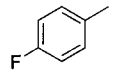
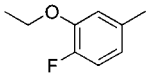
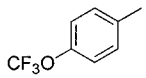
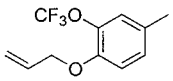
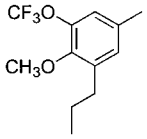
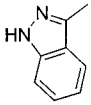
	Ar	Configuration %-ee R[a]	IC_{50} (μM)
51		racemic	5.4
52		95+%	4.9
53		95%	>30
54		racemic	2.7
55		racemic	5.5
56		>30%	18
57		>30%	>30
58		95+%	>30
59		95+%	> 30
60		95+%	5.5
61		95+%	10
62		95+%	12
63		racemic	1.6
64		>30%	0.30

[a] 95% and >30% are assigned on the basis of the methods of synthesis and their application to analogues in which optical purity was directly measured. [b] Previously reported by the Merck group (ref 7a).

The meta trifluoromethylated series appears refractory to the kinds of beneficial modifications seen in the aryl fluorides or the aryl trifluoromethoxy series. In analogue **47**, there is a detrimental effect upon addition of a second meta substitution (**46**). In a comparison of **47** with **48**, a hydrophobic ether function at the para

Table 2. Configuration and in Vitro *P. aeruginosa* LpxC Inhibition of Aroylserines



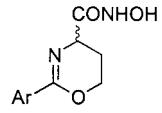
	Ar	Configuration %-ee R	IC_{50} (μM)
65		>95	>50
66		>95	3.9
67		>95	>50
68		>80	46
69		>85	1.54
70		>80	7.5
71		>95	>50
72		>95	13

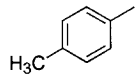
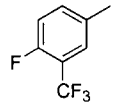
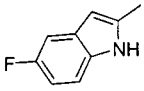
position fails to enhance activity significantly, even allowing for the fact that **48** is partially racemized, and this is in stark contrast to the 50-fold improvement in activity when one adds an allyloxy group to the trifluormethoxy compound **25** to give rise to **23**.

In the nonfluorinated analogues, the idea of an optimal chain length is suggested by comparing **19** (too short), **30** (too long), and **29**, **31** (intermediate length). Addition of a second aromatic ring is beneficial, with the benefits somewhat sensitive to the nature of the linkage (**32**−**34**). The idea that a second ring may access a critical binding site is reinforced by the comparison of **40** and **41**, in which a 10-fold loss of activity occurs upon shifting the trifluormethyl group in the benzyloxy ring from meta to ortho.

The similar, low micromolar IC_{50} values of the para trifluoromethoxy (**26**), nitro (**51**), dimethylamino (**52**), fluoro (**35**), bromo (**54**), and iodo (**55**) analogues suggest that the stringency for modest binders such as these is lower than for relatively strong binders. In this series, phenol **53** is strikingly inactive. Most of the active para

Table 3. In Vitro *P. aeruginosa* LpxC Inhibition of 2-Aryloxazines



	Ar	IC_{50} (μM)
73		>50
74		21.2
75		31.2

functional groups are potential hydrogen bond acceptors, and hydrogen bond acceptance may contribute to enzyme affinity.

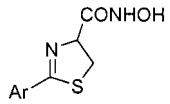
Heterocyclic aromatic groups in place of phenyl at the 2 position of the oxazoline varied widely in effects. The pyrazoles **58** and **59** were inactive up to 30 μM, whereas indole **63** was a good inhibitor whose activity was enhanced 5-fold upon further halogenation to **64**. Benzpyrazole **60**, a modest inhibitor, however, had its potency halved upon alkyl substitution at either N1 (**61**) or N2 (**62**). The potency of the meta-CF_3-substituted phenyl analogue **49** was not affected in the direct pyridyl homologue **50**.

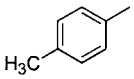
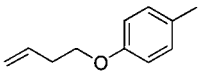
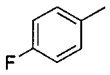
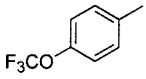
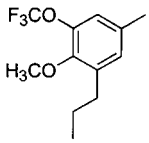
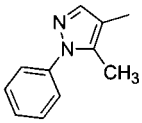
Since Schemes 2 and 4 enabled us to conveniently obtain the corresponding *N*α-aroyl-D-serine hydroxamic acids, these were also evaluated in vitro (Table 2). Thirty species were examined, with most showing no activity (IC_{50} > 50 μM). A portion of the data for acylserines appears in Table 2.

Oxazines. Although the trend we generally observed was that for any given aromatic nucleus the acylserine was less potent than the corresponding oxazoline, there were exceptions seen in analogue pairs **66**/**31** and **69**/**26**. We considered whether the increased flexibility of six-membered rather than five-membered ring might allow optimization of the relationship between the aromatic and hydroxamic acid moieties. Oxazines were prepared as direct analogues of a sampling of the oxazolines. We were disappointed to observe that these oxazines (Table 3) showed low activities against the *P. aeruginosa* LpxC.

Thiazolines. The thiazoline ring is found in a number of prokaryotic natural products, particularly where metal chelation is involved.[11a,e,18] We prepared a series of analogues incorporating aromatic substituents shown to be beneficial in oxazolines (as shown in Table 1) into the direct thiazoline analogues. As shown in Table 4, modest potency (17 μM) was achieved with **80**, the sulfur isostere of **5**, but in no case did the thiazolines approach the potency of the corresponding oxazolines.

Table 4. Configuration and in Vitro *P. aeruginosa* LpxC Inhibition of 2-Arylthiazolines



	Ar	Cα	IC_{50} (μM)
76		D	38.5
77		D	58.7
78		D,L	62.5
79		D,L	21.7
80		D	17.8
81		D	>60

Conclusions

Our efforts at expanding the original oxazoline hit resulted in the first reported inhibitors of the *P. aeruginosa* LpxC. Our strategy to retain the hydroxamic acid as the Zn binding function, but vary the heterocyclic and aromatic rings, enabled an in-depth exploration of the contribution of these two moieties to overall activity. The most active heterocyclic ring appeared to be the oxazoline. Ring expansion (oxazines) abrogated all activity, and with a few exceptions ring opening (acylserines) or sulfur substitution (thiazolines) gave rise to considerably weaker inhibitors. The highest inhibitory potencies came from aryl oxazolines with 3,4-disubstituted phenyl rings with fluoro or trifluoromethoxy in the para or meta position and a two- to five-atom hydrophobic group in the complementary position.

The foregoing would suggest that the electronic properties of the phenyl ring, the orientation of an oxygen lone pair, and a certain optimal hydrophobicity are the chief determinants of good inhibitory potency. The *m*-trifluoromethoxy function may be serving some or all of these functions. The SAR data to date suggest a somewhat restricted binding site in which the key contacts, including hydrogen bonding and lipophilic interactions, need to be made. In the absence of a CF_3O or F substituent, submicromolar potencies (**32**, **34**) could be achieved by optimizing the hydrophobic group at the para position. New libraries are under construction to refine the placement of these contacts.

Our best inhibitors are approaching the 100 nM range against isolated *P. aeruginosa* enzyme. Inhibitors in this range against the *E. coli* enzyme were reported to inhibit *E. coli* growth at MIC values ranging from 1.25 to 12.5 μg/mL.[5b] We are currently evaluating our novel compounds against a panel of Gram-negative organisms, both wild-type and selected mutants, to obtain MIC profiles and thereby to validate the concept of LpxC inhibitors as therapeutic agents.

Experimental Section

General. Unless otherwise indicated, all anhydrous solvents were commercially obtained and stored in Sure-seal bottles under nitrogen. All other reagents and solvents were purchased as the highest grade available and used without further purification. Ethereal diazomethane was used for the production of methyl esters. It was prepared by adding a gram of *N*-nitroso-*N*-methylurea in small portions to an ice-cold mixture of 4 mL of 40% aqueous KOH and 8 mL of Et_2O. After 5 min, the resulting ether layer was briefly dried over a few KOH pellets and the solution was added in 1 mL aliquots to the acid dissolved in ether containing up to 20 vol % MeOH as required for solubilization. NMR spectra were recorded on Bruker 400 or 500 MHz instruments. Chemical shifts (δ) are reported in parts per million (ppm) referenced to ^1H (Me_4Si at 0.00), ^{13}C (DMSO at 39.55, $CDCl_3$ at 77.0, and CD_3OD at 49.0), and ^{19}F (50 μM TFA at −76.55). All ^{19}F spectra were recorded at 470.3 MHz in pH 7 aqueous buffer. Coupling constants (J) are reported in Hz throughout. Mass spectral data were acquired on a Esquire LC00066 for low resolution, a Micromass 70 SEQ for high resolution, or a JEOL LC-mate tuned for either low resolution or high resolution. Optical rotations were determined on a Perkin-Elmer model 241 polarimeter. Circular dichroic (CD) spectra over the 325−205 nm wavelength range were recorded for ca. 1 mM solution in CH_3OH at 20 °C in a 1 mm path length cell using a JASCO model J720 spectropolarimeter with a nitrogen flow rate of 5 L/min. CD data are reported as molar ellipticity ($[\theta]_\lambda$ in units of deg cm^2 $dmol^{-1}$) at the near-UV extremum (λ in nm) corresponding closely to the UV maximum.

All parallel synthesis was conducted on a Quest 210 synthesizer equipped with an automated solvent washing module and a gaseous reaction and concentration module (Argonaut Technologies, San Carlos, CA) under an atmosphere of dry nitrogen. All single syntheses were conducted in conventional flasks under an atmosphere of dry nitrogen. For parallel synthesis, evaporation of volatiles in vacuo was done on a Savant SC210A Speedvac at ca. 0.9 Torr; for single synthesis, evaporation of volatiles in vacuo was done on a vacuum-driven Buchi rotavapor at ca. 15 Torr followed by vacuum-drying at ca. 0.5 Torr. Analytical HPLC was conducted on a Gilson, Varian, or a Waters instrument using a 2.5 mm × 250 mm octadecylsilane (ODS) column, 10 μm, 100 Å, at a flow rate of 1.0 mL/min. Unless otherwise indicated, peaks were monitored at 254 and 215 nM. Preparative high-performance liquid chromatography (HPLC) was conducted on a Varian model 210 using a 10 mm × 250 mm ODS column, 5 μm, 100 Å, at a flow rate of 4.6 mL/min. Peaks were monitored at 260 and 215 nM. Radial chromatography was performed on a Chromatotron instrument (Harrison Research, Palo Alto, CA) using EM Science silica gel as adsorbent; preparative thin-layer chromatography experiments were done on VWR GF silica gel plates, and all other preparative normal phase chromatography experiments were done on either flash or Biotage systems. Radiochemical synthesis was performed at the Lawrence Berkeley Laboratory (Berkeley, CA) with the assistance of the LBL staff.

6-Propyl-2-trifluoromethoxyphenol (1). To a solution of 2-trifluoromethoxyphenol (3.0 g, 16.12 mmol) in freshly dis-

tilled acetone (100 mL) was added solid K_2CO_3 (4.7 g, 33.7 mmol) and allyl bromide (4.08 g, 33.7 mmol), and the reaction mixture was refluxed for 3 h, then cooled to ambient temperature and concentrated in vacuo. The residue was dissolved in CH_2Cl_2, and the organic phase was washed sequentially with water, saturated Na_2CO_3, and saturated brine, dried, and concentrated in vacuo to give the allyl ether (3.13 g, 14.4 mmol, 85%) as a light-yellow oil that required no further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (H-3, m), 7.22 (H-5, td, 8, 1.5), 6.98 (H-6, dd, J = 8, 1.5), 6.94 (H-4, td, 8, 1.5), 6.04 (ddt), 5.44 (dq, J_d = 16), 5.30 (dq, J_d = 10) (−CH═CH_2), and 4.60 (OCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.09 (C2), 138.39 (C1), 132.57 (C2′), 127.93 (C4), 123.52 (C5), 120.96 (C6), 120.76 (OCF_3, q, 257.0), 117.51 (C3′), 114.46 (C3), 69.22 (C1′); MS, m/z 216.9 $(M - H)^-$.

A solution of the above allyl ether (3.13 g, 14.4 mmol) in *N*,*N*-dimethylaniline (25 mL) was refluxed for 7 h, then cooled to ambient temperature and poured into a mixture of ethyl acetate over ice-cold 50% HCl (80 mL). The organic phase was separated and washed with saturated brine, dried, and concentrated in vacuo to give the *o*-allylphenol (3.3 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (H-3, d quint, J = 8, 1), 7.07 (H-5, ∼d, J = 8), 6.86 (H-4, t, J = 8), 6.00 (CH═C, m), 5.42 (OH), 5.09−5.13 (2H, C═CH_2), 3.45 (CH_2, d, J = 7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.69 (C1), 136.44 (C2), 135.78 (C1′), 128.46 (C6), 120.49 (OCF_3, q, 258.8), 120.10 (C4), 118.96 (C3), 116.28 (C3′), 34.06 (C1′); MS, m/z 216.8 $(M - H)^-$.

The Claisen product was dissolved in EtOH (200 mL) and hydrogenated over 10% Pd−C (300 mg) at 1 atm for 3 h. Filtration through Celite and concentration of the filtrate in vacuo gave **1** (3.1 g, 14.1 mmol, 98%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (H-3,5, ∼t), 6.84 (H-4, t), 5.32 (OH, br s), 2.65 (2H, t), 1.66 (2H, sextet), 0.96 (CH_3, t); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.72 (C1), 136.38 (C2), 131.37 (C5), 128.38 (C6), 120.77 (OCF_3, q, J = 258.5), 119.74 (C4), 118.29 (C3), 31.85 (C1′), 22.59 (C2′), 13.84 (C3′).

4-Methoxy-5-propyl-3-trifluoromethoxybenzoic Acid (2a). To a −78 °C solution of **1** (3.1 g, 14.1 mmol) in CH_2Cl_2 (200 mL) was added Br_2 (2.48 g, 15.5 mmol) dropwise via syringe. Upon completion of the Br_2 addition the reaction mixture was warmed to − 5 °C, stirred at this temperature for 4 h, then allowed to warm to ambient temperature overnight. The reaction mixture was treated with saturated $Na_2S_2O_5$ (100 mL), stirred for 5 min, then partitioned between CH_2Cl_2 and water. The organic phase was separated, dried, and concentrated in vacuo to give the 4-bromophenol intermediate (3.5 g, 11.8 mmol, 83%) as a colorless oil that solidified on standing: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23, 7.21 (H-3,5), 2.60 ($ArCH_2$, ∼t), 1.64 (CH_2, sextet), 0.96 (CH_3, t); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.96 (C1), 136.41 (C2), 133.17 (C5), 131.00 (C6), 122.50 (C3), 120.58 (OCF_3, q, J = 260.2), 111.05 (C4), 31.68 (C1′), 22.46 (C2′), 13.79 (C3′); MS, m/z 297.0, 299.0 $(M - H)^-$.

Solid K_2CO_3 (1.62 g, 11.8 mmol) was flame-dried under nitrogen in a flask. The product of the above reaction in freshly distilled acetone (100 mL) was added, followed by addition of methyl iodide (1.7 g, 11.8 mmol). The reaction mixture was refluxed for 6 h, stirred at ambient temperature overnight, then filtered and concentrated in vacuo. The residue was partitioned between $CHCl_3$ and water, and the organic phase was separated, dried, and concentrated in vacuo to give the methyl ether (3.4 g, 10.9 mmol, 93%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (H-2,6, s), 3.85 (OCH_3 s), 2.58 ($ArCH_2$, ∼t), 1.61 (CH_2, sextet), 0.97 (CH_3, t); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.99 (C4), 142.88 (C3), 140.08 (C6), 131.65 (C5), 122.15 (C2), 119.58 (OCF_3, q), 115.73 (C1), 61.75 (OCH_3), 32.11 (C1′), 23.89 (C2′), 14.28 (C3′); MS, m/z 311.2, 313.1 $(M - H)^-$.

To a 78 °C solution of the above intermediate (1.40 g, 4.47 mmol) in anhydrous ether (45 mL), a 1.6 M solution of *n*-butyllithium (3.2 mL, 5.12 mmol) in hexane was added dropwise. The reaction mixture was stirred at − 78 °C for 1 h before the cooling bath was removed. Carbon dioxide gas was bubbled vigorously through the reaction mixture for 1.5 h as the reaction mixture warmed to −10 °C. The reaction was quenched by the addition of 30 mL of 1 M NaOH followed by the addition of 30 mL of CH_2Cl_2. The resulting aqueous layer was washed with an additional 30 mL portion of CH_2Cl_2, acidified with 6 N HCl, and extracted with EtOAc (3 × 60 mL). The organic phase was washed with saturated brine, dried, and concentrated in vacuo, affording acid **2a** (520 mg, 42%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.882 (6H, d, J = 2), 7.855 (2H, dq, J = 2, 1), 3.96 (OMe, s), 2.671 (2H, d, J = 7.7), 1.65 (2H, sextet, J = 7.7), 0.98 (3H, t, J = 7.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.45 (COOH), 154.81 (C4), 141.31 (C3), 137.82 (C6), 130.23 (C5), 124.23 (C1), 121.97 (C2), 120.34 (OCF_3, q, J = 258.6), 61.22 (OCH_3), 31.79 (C1′), 23.04 (C2′), 13.45 (C3′); MS, m/z 276.9 $(M - H)^-$.

2-(4-Methoxy-3-propyl-5-trifluoromethoxyphenyl)-4,5-dihydrooxazole-4-carboxylic Acid Methyl Ester (4a). To a suspension of D-serine methyl ester hydrochloride (0.35 g, 2.3 mmol) in CH_2Cl_2 (50 mL) was added sequentially **2a** (0.5 g, 1.9 mmol), EDCI (0.65 g, 3.4 mmol), and DIEA (0.59 mL, 3.4 mmol) [condensation method B]. The reaction mixture was stirred at ambient temperature overnight, then washed sequentially with water, 0.5 N HCl, saturated $NaHCO_3$, and brine. The organic phase was dried and concentrated in vacuo to give **3a** (553 mg, 1.5 mmol, 77%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16−7.20 (H-2,6), 4.867 (Hα, dt, J = 7, 3.5), 4.098/4.057 ($C_\beta H_2$, AB of ABX, ^2J = 11.5, ^3J = 3.8/3.2), 3.91 (OCH_3, s), 3.83 (OCH_3,s), 2.64 ($ArCH_2$, AB m), 1.62 (CH_2, m), 0.96 (CH_3, t); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.83 (CO_2R), 165.93 (CONH), 153.17 (C4), 141.52 (C3), 137.95 (C6), 128.64 (C5), 127.06 (C1), 120.27 (OCF_3, q, J = 258.6), 119.41 (C2), 62.83 (CH_2OH), 61.16 (Ar−OCH_3), 55.14 (CH), 53.02 (CO−OCH_3), 31.68 (C1′), 23.08 (C2′), 13.69 (C3′).

To a solution of **3a** (553 mg, 1.5 mmol) in anhydrous THF (12 mL) in a pressure tube was added Burgess reagent (383 mg, 1.60 mmol). The tube was flushed with nitrogen, sealed, and heated to 70 °C for 2.5 h. The reaction was cooled to ambient temperature, and the solution was concentrated in vacuo to an oily residue. Chromatography on silica (90:10 hexane/ethyl acetate as eluant) gave ester **4a** (254 mg, 0.7 mmol, 49%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.778 (H-5, d, J = 2), 7.710 (H-2, dq), 4.944 (1H, dd, J = 10.5, 8), 4.694 (1H, ∼t, J = 8.3), 4.589 (1H, dd, J = 10.5, 8.5), 2.635 (2H, AB m), 1.627 (2H, sextet), 0.956 (3H, t, J = 7.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.54 (CO_2R), 163.12/66.71/67.79 (oxaz-C2,4,5), 151.45 (C4), 139.68 (C3), 136.12 (C6), 126.93 (C5), 120.93 (C1), 119.89 (C2), 119.58 (OCF3, q), 59.50 (Ar−OCH_3), 50.83 (CO−OCH_3), 30.02 (C1′), 21.66 (C2′), 12.0 (C3′); MS, m/z 362.1 $(M + H)^+$.

2-(4-Methoxy-5-propyl-3-trifluoromethoxyphenyl)-4,5-dihydrooxazole-4-carboxylic Acid Hydroxamide (5). To an ice-cooled suspension of benzyloxyamine hydrochloride (146 mg, 0.97 mmol) in anhydrous benzene (1.5 mL) was added a 2 M solution of trimethylaluminum in toluene (0.44 mL, 0.88 mmol). The resulting solution was stirred at ambient temperature for 90 min, then transferred via cannula to a solution of **4a** (254 mg, 0.70 mmol) in anhydrous benzene (2 mL). The reaction mixture was heated to 50 °C for 5.5 h, then cooled to ambient temperature, quenched by addition of water (200 μL), and stirred for 10 min. After the insoluble material was filtered off, the filtrate was partitioned between ethyl acetate and water, and the organic phase was dried and concentrated in vacuo to give the benzyloxy intermediate (280 mg, 0.62 mmol, 89%, MS, m/z 453.2), which was dissolved in 22 mL of methanol and hydrogenated over 20% $Pd(OH)_2$ (50 mg) at 1 atm for 1 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo to give 250 mg of the crude product as an off-white solid. Purification on silica gel (60:40 hexane/ethyl acetate as eluant) followed by precipitation with hexane gave **5** (85 mg, 0.24 mmol, 39%): mp 140−143 °C; $[\alpha]^{25}_D$ −49.00° (*c* 0.1, CH_3OH), CD $[\theta]_{253}$ = −12 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.4−9.5 (NH, br), 7.6−7.7 (H-2,6), 4.8−4.9 (Hα, ∼t), 4.46−4.7 ($C\beta H_2$, AB pattern), 3.9 (OCH_3, s), 2.6−2.7 ($ArCH_2$, t), 1.6 (CH_2, sextet), 0.9 (CH_3, t); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.33 (CONHOH), 167.73 /69.23/72.23 (oxaz-C2,4,5), 155.56 (C4), 143.53 (C3), 140.13 (C6), 123.62 (C1), 122.28 (C2), 63.35 (OCH_3), 33.47 (C1′), 24.35 (C2′), 15.80 (C3′); ^{19}F NMR δ −58.92;

MS, *m/z* 363 $(M + H)^+$. Anal. found C 49.50, H 4.30, N 7.53; calcd for $C_{15}H_{17}F_3N_2O_5$, C 49.73, H 4.73, N 7.73.

General Procedure for the Solid-Phase Parallel Synthesis of Oxazoline Hydroxamic Acids. Into 10 10 mL reaction vessels was dispensed fluorenemethyleneoxycarbonyl (Fmoc)-aminoxy-*o*-chlortritylpolystyrene (0.58 g, 0.39 mmol per reaction vessel, from a 0.6 mmol/g, Advanced ChemTech batch), and the resins were treated three successive times with 20% piperidine in DMF for 1 h, each time followed by a DMF wash, to remove the Fmoc group. The resins were washed one final time with, successively, DMF (3×), MeOH (3×), and CH_2Cl_2 (3×). The reaction block was cooled to 0 °C, and to each reaction vessel was added a solution of either Fmoc-D-serine (0.13 g, 0.4 mmol) or Fmoc-D-threonine (0.14 g, 0.4 mmol) in 2 mL of anhydrous DMF, followed by a solution of HATU (0.27 g, 0.7 mmol) and DIEA (0.14 mL, 0.8 mmol) in 2 mL of anhydrous DMF. The reaction block was equilibrated to ambient temperature, and the vessels were agitated for 16 h, then washed using the three-solvent wash protocol described above. The Fmoc group was removed under the standard reaction and wash conditions described above, followed by treatment of each individual reaction vessel with a solution of an arylcarboxylic acid (0.42 mmol), HATU (0.16 g, 0.42 mmol), and DIEA (0.09 mL, 0.5 mmol) in 4 mL of anhydrous DMF, agitation for 16 h at ambient temperature, and washing as described above. The resin was suspended in CH_2Cl_2, the reaction block cooled to −15 °C, and DAST (0.22 mL, 1.7 mmol) added via syringe. Agitation was continued for 1 h at −15 °C, and the reaction was then quenched by addition of excess aqueous NH_4OH. The reaction block was equilibrated to ambient temperature, and the resins were washed as above. To release the products from the resin, 10% TFA in CH_2Cl_2 (5.0 mL) was added and the resins were agitated for 90 min. Filtrates from each reaction vessel were drained into vials and concentrated in vacuo. The crude oxazoline hydroxamic acids were purified by preparative thin-layer chromatography using 3% MeOH in CH_2Cl_2 as eluant. Yields were ca. 50%. All products from the solid-phase library were characterized by proton NMR and mass spectrometry and were shown to be >90% pure by reverse-phase HPLC.

Representative 2-Aryloxazoline-4-hydroxamic Acids Prepared by Solid-Phase Methods. 2-*p*-Tolyloxazoline-4-hydroxamic acid (19): ^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD) δ 7.82 (2H, d, J = 8.1), 7.25 (2H, d, J = 8.1), 4.76 (1H, t, J = 10.3), 4.65 (1H, t, J = 9.8), 4.57 (1H, t, J = 10.3), 2.40 (3H, s); MS, *m/z* 221.0 $(M + H)^+$.

2-(3-Trifluoromethoxyphenyl)oxazoline-4-hydroxamic acid (25): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.40−7.92 (4H, m), 4.73−4.78 (1H, m) 4.33−4.60 (2H, m); MS, *m/z* 291.0 $(M - H)^-$.

2-(4-Trifluoromethoxyphenyl)oxazoline-4-hydroxamic acid (26): CD $[\theta]_{246} = -12\,400$; ^{1}H NMR (DMSO-$d_6$) δ 10.9 and 9.03 (CONHOH), 8.01 (H-3,5, d, J = 8.7), 7.49 (H-2,6, d), 4.70/4.59/4.52 ($CHCH_2$); MS, *m/z* 291.0623 $(M + H)^+$, calcd for $C_{11}H_{10}F_3N_2O_4$, 291.0593; $[\alpha]^{25}_D$ −46.62° (*c* 0.21, CH_3OH). Prepared also by Scheme 4 (methods C and F): mp 181−182°C; CD $[\theta]_{246} = -16\,000$; ^{13}C NMR δ 166.94 (CONHOH), 163.06/66.91/69.98 (oxaz-C2,4,5), 163.06 (CONHOH), 150.67 (C4), 130.37 (C2,6), 126.09 (C1), 120.00 (OCF_3, q, ^1J = 257.7), 120.99 (C3,5); ^{19}F NMR δ −58.65; MS, *m/z* 291.02 $(M + H)^+$, 313.0 $(M + Na)^+$. Anal. found C 45.45, H 2.89, N 10.22; calcd for $C_{11}H_9F_3N_2O_4$, C 45.53, H 3.13, N 9.65. Compound **26** was also prepared by methods B and D: CD $[\theta]_{246} = -18\,600$.

2-(2-Trifluoromethoxyphenyl)oxazoline-4-hydroxamic acid (28): ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (1H, m), 7.92 (1H, m), 7.69−7.76 (2H, m), 4.96−5.10 (1H, m), 4.89−4.94 (2H, m); MS, *m/z* 291.1 $(M + H)^+$.

2-(5-Methyl-1-phenyl-(1*H*)-pyrazol-4-yl)oxazoline-4-hydroxamic acid (58): ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (1H, s), 7.63−7.45 (5H, m), 5.21−5.13 (1H, m), 4.96−4.82 (2H, m), 2.57 (3H, s); MS, *m/z* 287.2 $(M + H)^+$.

2-(5-Trifluoromethyl-1-phenyl-(1*H*)-pyrazol)-4-ylhydroxamic acid (59): ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (H_{pyr}, s), 7.23−7.53 (H_{phenyl}, m), 4.48−4.87 ($CH_2\beta$ and CHα, m); MS, *m/z* 341.0 $(M + H)^+$.

General Procedure for the Solid-Phase Parallel Synthesis of Acylserine Hydroxamic Acids. To obtain the acyclic analogues, the resin-bound acylserine, prepared as described above, was subjected directly to the TFA cleavage following the washing protocol. Purification of the crude acylserine hydroxamic acids was by radial or preparative thin-layer chromatography using 3% MeOH in CH_2Cl_2 as eluant. Determinations of purity and structure were the same as for the oxazolines.

Representative *N*α-Aroylserine Hydroxamic Acids Prepared by Solid-Phase Methods. *N*-(4-Methylbenzoyl)-serine hydroxamic acid (65): ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (2H, d, J = 8.1), 7.19 (2H, d, J = 8.1), 4.61−4.44 (1H, m), 3.95−3.78 (2H, m), 2.25 (3H, s); MS, *m/z* 239.0 $(M + H)^+$.

***N*-[4-(But-3-enyloxy)benzoyl]serine hydroxamic acid (66):** ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (2H, d, J = 8.7), 6.98 (2H, d, J = 8.7), 5.96−5.88 (1H, m), 5.17 (1H, dd, J = 17.2, 1.6), 5.09 (1H, dd, J = 11.7, 1.6), 4.57 (1H, bs), 4.08 (2H, t, J = 6.6), 3.86 (2H, d, J = 4.7), 2.54 (2H, q, J = 6.6); MS, *m/z* 295.1 $(M + H)^+$.

***N*-(7 Benzpyrazolyloyl)serine hydroxamic acid (72):** ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (1H, d, J = 8.2), 7.61 (1H, d, J = 8.5), 7.45 (1H, t, J = 7.2), 7.29 (1H, t, J = 7.6), 4.65 (1H, bs), 3.95−3.81 (2H, m); MS, *m/z* 265.1 $(M + H)^+$.

Bromophenols 9 (Scheme 3). The example $R_F = CF_3O$, R = H is representative of the general bromination procedure. To a solution of 2-trifluoromethoxyphenol (7.40 g, 41.5 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added a bromine solution (45 mL, 1.0 M, 45 mmol) in CH_2Cl_2 dropwise over 20 min. The reaction was allowed to warm to ambient temperature and stirred for 48 h. Saturated Na_2SO_3 (100 mL) was added, and the reaction mixture was stirred vigorously until disappearance of the orange color was observed. The biphasic mixture was diluted with CH_2Cl_2 (200 mL), and the organic layer was separated, washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo to give 9.80 g (93%) of a white solid: mp 50−52 °C (sublimed); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (H-3, dq, J = 2.0, 1.1), 7.32 (H-5, dd, J = 8.9, 2.0), 6.95 (H-6, d, J = 8.9).

If the bromination was carried out with added KOAc to accelerate the process or with excess bromine, 4,6-dibromo-2-trifluoromethoxyphenol was obtained as a major byproduct: mp 39−41 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.615 (H-5, d, J = 1.9), 7.38 (H-3, dq, J = 2, 1). For phenols with only a single available ortho or para position, the addition of KOAc allowed the reaction to go to completion in a few hours at ambient temperature. 4-Bromo-2-fluoro-, 4-bromo-2-trifluoromethyl-, and 4-bromo-2-fluoro-5-methylphenol were prepared in the same manner.

5-Bromo-3-fluoro-4-methoxybenzoic Acid (13, R_F = F, R = H). Bromine (3.1 mmol, 1.05 equiv) was added dropwise with stirring over 30 min to an ice-cooled solution of methyl 3-fluoro-4-hydroxybenzoate[19] (0.5 g, 2.94 mmol) and 6 mL of 1:1 CH_2Cl_2/AcOH. After being stirred overnight at room temperature, the mixture was diluted with the ethyl acetate (20 mL) and the resulting solution was aqueous Na_2SO_3, water, and brine and was dried over $MgSO_4$. Evaporation in vacuo afforded (84% yield) methyl 5-bromo-3-fluoro-4-hydroxybenzoate as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (H-6, dd J = 1.8, 1.5), 7.76 (H-2, dd, J = 10.3, 1.5), 6.01(OH), 3.88 (3H, s). Methylation by the standard procedure: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (H-6, dd, J = 1.8, 1.4), 7.67 (H-2, dd, J = 11.7, 1.8), 4.03 ($ArOCH_3$, d, J_F = 2.5), 3.88 ($COOCH_3$, s). Methylation followed by saponification afforded the title acid in 71% overall yield: mp 158−160 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (H-6), 7.76 (H-2, dd, J = 11.6, 2), 3.98 (3H, bs).

3-Alkyl-4-fluorobenzoic Acids 14 (R′ = Propyl Is Representative). A solution of methyl 3-bromo-4-fluorobenzoate (1.080 g, 4.634 mmol) in DMF (13 mL) was added to a pressure tube containing tetrakis(triphenylphosphine)palladium(0) (350 mg, 0.302 mmol). Allyltributyltin (1.8 mL, 5.8 mmol) was

added, the solution was purged with a stream of nitrogen for 5 min, and the pressure tube was sealed. The reaction mixture was heated at 85 °C for 40 h, cooled, and filtered through a plug of SiO_2 eluting with Et_2O (200 mL). The organic layer was washed with H_2O (5 × 80 mL) and brine (80 mL), dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica gel (100% hexanes) afforded 1.46 g of a yellow oil consisting of methyl 3-allyl-4-fluorobenzoate and Bu_3SnBr, which was dissolved in EtOH (15 mL), treated with 10% Pd−C (310 mg), and stirred under a hydrogen atmosphere (ambient pressure) for 16 h. The reaction mixture was filtered through a pad of Celite eluting with CH_2Cl_2 (100 mL), concentrated, and then filtered through a plug of silica gel eluting with 10:1 hexanes/EtOAc (150 mL). The organic layer was concentrated in vacuo to give a colorless oil, which was dissolved in a mixture of THF (14 mL), MeOH (2 mL), and H_2O (6 mL). Aqueous KOH (2.5 mL, 6 M, 15 mmol) was added, and the reaction was stirred overnight. The solution was concentrated to a volume of ca. 5 mL, H_2O (45 mL) was added, and the aqueous layer was washed with Et_2O (2 × 50 mL). The organic layer was discarded, and the aqueous layer was acidified with 6 M HCl (5 mL) and extracted with CH_2Cl_2 (3 × 30 mL), and the organic layer was dried over $MgSO_4$. Concentration in vacuo gave 648 mg (77%, three steps) of acid **14** (R′ = Pr), a white powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99−7.93 (H-2,6, m), 7.09 (H-5, t, J = 9.0), 2.67 ($ArCH_2$, t, J = 7.5), 1.68 (CH_2, sextet, 8.0), 0.97 (CH_3, t, J = 7.5).

In a subsequent reaction from methyl 3-bromo-4-fluorobenzoate (11 mmol), the saponification was performed on the 3-allylbenzoate, affording 1.77 g (89% in three steps) of acid **14** (R′ = allyl) as a white solid: mp 95−96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01−7.97 (H-2,6, m), 7.12 (H-5, t, J = 9.0), 6.01−5.92 (CH═C, m), 5.16−5.09 (C═CH_2, m), 3.46 ($ArCH_2$, d, J = 6.0).

Representative Procedures for Solution-Phase Syntheses of 2-Phenyloxazoline Hydroxamic Acids (Scheme 4). Method A. *N*-(3-Ethoxy-4-fluorobenzoyl)-D-serine Methyl Ester (3, Ar = 3-OEt−4-F−phenyl). To a solution of 3-ethoxy-4-fluorobenzoic acid (177 mg, 0.961 mmol), d-serine methyl ester hydrochloride (179 mg, 1.15 mmol), HATU (420 mg, 1.10 mmol), and HOAt (131 mg, 0.962 mmol) in DMF (3 mL) at 0 °C was added DIEA (370 μL, 2.2 mmol), and the solution was stirred for 16 h, slowly warming to ambient temperature. The reaction mixture was diluted with ethyl acetate (75 mL) and washed with 1 M HCl (2 × 20 mL), saturated $NaHCO_3$ (2 × 20 mL), and H_2O (4 × 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 245 mg (89%) of a pale-yellow oil, which slowly solidified to give a white solid: mp 111−112°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (H-2, dd, J = 2.0, 8.0), 7.32 (H-6, ddd, J = 2.0, 4.0, 8.5), 7.12 (H-5, dd, J = 8.5, 10.5), 7.02 (NH, d, J = 6.5), 4.86 (1H, dt, J = 3.5, 7.0), 4.17 (2H, q, J = 7.0), 4.12−4.03 (2H, m), 3.84 (3H, s), 2.39 (OH, t, J = 6.0), 1.47 (3H, t, J = 7.0).

Method B. *N*-[3-Fluoro-4-(3′-trifluoromethylbenzyloxy)-benzoyl]-D-serine Methyl Ester [3, Ar = 3-F, 4-(3′-Trifluoromethylbenzyloxy)phenyl]. To a solution of 4-(3′-trifluoromethylbenzyloxy)-3-fluorobenzoic acid (200 mg, 0.63 mmol) in 4 mL of DMF was added, sequentially, D-serine methyl ester HCl (90 mg, 0.58 mmol), EDCI (120 mg, 0.63 mmol), HOAt (77 mg, 0.57 mmol), and DIEA (0.23 mL, 13.3 mmol). The mixture was stirred at room temperature for 16 h, then diluted with ethyl acetate (15 mL) and washed sequentially with 1 M HCl (3 × 5 mL), saturated $NaCO_3$ (3 × 5 mL), water (5 mL), and brine (5 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was evaporated to give 210 mg (79%) of the title ester as an oil that required no further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (1H, s), 7.62−7.67 (2CH, NH), 7.59 (1H, ddd), 7.55 (1H, t), 7.04 (2H, ∼t), 5.25 (2H, s), 4.87 (Hα, dt, J = 7.1, 3.6), 4.08 (AB of ABX, $\Delta\delta_{AB}$ = 0.042, J_{AB} = 11.2), 3.84 (3H, s).

Method C. *N*-[3-Propyl-4-fluorobenzoyl]-D-serine Methyl Ester (3, Ar = 3-Pr−4-F−phenyl). To a suspension of **14**(R′ = Pr) (364 mg, 2.00 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added oxalyl chloride (188 μL, 2.15 mmol) and DMF (7 μL). The reaction mixture was warmed gradually to ambient temperature over 1 h and then recooled to 0 °C. A solution of D-serine methyl ester hydrochloride (334 mg, 2.15 mmol) and DIEA (1.1 mL, 6.3 mmol) in CH_2Cl_2 was added dropwise over 5 min, and the reaction mixture was stirred 16 h, slowly warming to ambient temperature. The reaction mixture was concentrated and filtered through a plug of silica gel, eluting with CH_2Cl_2/MeOH (15:1) and concentrated to give a 560 mg of a yellow oil that was used directly in the cyclization reaction.

General Procedure for Cyclization. 2-(3-Propyl-4-fluorophenyl)-4,5-dihydrooxazole-4-carboxylic Acid Methyl Ester (4, Ar = 3-Pr−4-F−phenyl). The acylserine intermediate described immediately above was dissolved in CH_2Cl_2 (6 mL) and cooled to −20 °C. A solution of DAST (2.0 mL, 1.0 M, 2.0 mmol) in CH_2Cl_2 was added, and the solution was stirred for 30 min at −20 °C. One additional equivalent of DAST (2.0 mL, 1.0 M, 2.0 mmol) was added, and the reaction mixture was stirred for 1 h. Saturated $NaHCO_3$ (15 mL) was added, the solution warmed to ambient temperature, and the reaction mixture diluted with CH_2Cl_2 (60 mL). The organic layer was separated, washed with 1 M HCl (30 mL), dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil. Purification by silica gel chromatography (100:1 CH_2Cl_2/MeOH) afforded 475 mg (90% over two steps) of the methyl oxazoline-4-carboxylate as a pale-yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (H-2, dd, J = 2.5, 7.5), 7.79 (H-6, ddd, J = 2.5, 5.0, 9.0), 7.03 (H-5, t, J = 10.0), 4.94 (1H, dd, J = 8.0, 10.5), 4.69 (1H, t, J = 9.0), 4.59 (1H, dd, J = 8.5, 10.5), 3.85 (3H, s), 2.64 (2H, m), 1.64 (2H, sextet, J = 7.5), 0.94 (3H, t, J = 7.5).

In like manner, *N*-(3-ethoxy-4-fluorobenzoyl)-D-serine methyl ester (161 mg, 0.564 mmol) was cyclized affording 147 mg (98%, crude) of the oxazoline carboxylate: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (H-2, dd, J = 2.0, 8.0), 7.53 (H-6, ddd, J = 2.0, 4.5, 8.5), 7.10 (H-5, dd, J = 8.5, 11.0), 4.94 (1H, dd, J = 7.5, 10.5), 4.69 (1H, t, J = 8.3), 4.59 (1H, dd, J = 9.0, 10.5), 4.15 (2H, m), 3.83 (3H, s), 1.46 (3H, 7.0).

Method F (Illustrated with the Synthesis of Hydroxamic Acids 38 and 44). 2-(3-Propyl-4-fluorophenyl)-4,5-dihydrooxazole-4-carboxylic Acid Hydroxamic Acid (38). To a solution of hydroxylamine hydrochloride (138 mg, 1.99 mmol) in anhydrous MeOH (2.0 mL) at 0 °C was added sodium methoxide (737 mg, 25 wt % in MeOH, 3.4 mmol). Methyl ester **4** (Ar = 3-Pr−4-F−phenyl, 471 mg, 1.78 mmol) in MeOH (2.0 mL) was added, and the solution was stirred at 0 °C for 5 h. The reaction mixture was quenched with H_2O (4 mL) and 1 M HCl (5.0 mL), cooled to 0 °C, and filtered to give 343 mg (73%) of partially racemized **38** as a white solid: mp 163−165°C; CD $[\theta]_{246}$ = −10 800 (74% ee); MS, m/z 267 $(M + H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.87 and 9.01 (CONHOH, 2 s), 7.82 (H-2, dd, J = 2.0, 7.5), 7.78−7.74 (H-6, m), 7.26 (H-5, t, J = 9.0), 4.66 (1H, dd, J = 8.0, 9.5), 4.55 (1H, t, J = 8.5), 4.48 (1H, t, J = 8.0), 2.63 (2H, t, J = 7.0), 1.58 (2H, sextet, J = 7.0), 0.90 (3H, t, J = 7.0); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 167.08 (CONHOH), 163.39/66.83/69.75 (oxaz-C2,4,5), 162.61 (C4, d, ^1J = 248.9), 130.95 (C2, d, ^3J = 5.0), 129.20 (C3, d, ^2J = 17.6), 128.11 (C6, d, ^3J = 8.8), 123.31 (C1), 115.63 (C5, d, ^2J = 23.9), 30.05 (C1′), 22.73 (C2′), 13.51 (C3′); ^{19}F NMR δ −113.18.

In like manner, 142 mg of ester **4** (Ar = 3-EtO−4-F−phenyl) afforded 61 mg (43%) of **44** as a white solid: mp 160−162 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.82 and 9.01 (CONHOH), 7.60 (H-2, dd, J = 2.0, 8.0), 7.46 (H-6, ddd, J = 2.0, 4.5, 8.5), 7.33 (H-5, dd, J = 8.5, 11.0), 4.68 (1H, dd, J = 7.5, 10.0), 4.56 (1H, dd, J = 8.5, 10.0), 4.49 (1H, t, J = 8.0), 4.15 (2H, q, J = 7.0), 1.37 (3H, t, J = 7.0); MS, m/z 269.0948 $(M + H)^+$, calcd for $C_{12}H_{14}FN_2O_4$, 269.0938.

In a subsequent experiment, the optically pure *R* enantiomer, (−)-**38**, was prepared from **14** (R′ = allyl) using the same cyclization method but installing the hydroxamate function by method D with hydrogenation of the allyl group occurring during the hydrogenolysis of the benzyloxyamide: CD $[\theta]_{246}$ = −14 600; MS, m/z 267.1146 $(M + H)^+$, calcd for $C_{13}H_{16}FN_2O_3$,

267.1145. NMR spectra matched those previously recorded for the partially racemized sample.

General Procedures for the Solution-Phase Parallel Synthesis of Oxazoline Hydroxamic Acids. All of the methods shown in Scheme 4 were amenable to parallel synthesis. The following examples are illustrative.

Methods A and E. Individual aromatic carboxylic acids (2.2 mmol acid) were dispensed into 10 mL reaction vessels, and to each was added 2.4 mL of a DMF solution that was 0.83 M in D-serine methyl ester HCl and 0.92 M in HOAt (or HOBt). The reaction vessels were positioned on the Quest, flushed with nitrogen, and cooled to 4 °C, and to each was added, with gentle agitation, a 0.55 M solution of HATU in DMF (4 mL) followed by DIEA (4.4 mmol, 766 μL). The reaction vessels were brought to ambient temperature and agitated under a nitrogen atmosphere for 16 h. Each reaction vessel was drained into a vial, the volatiles were removed in vacuo, and the residues were dissolved in ethyl acetate and individually washed successively with 0.5 N HCl, saturated $NaHCO_3$, and saturated brine. Each ethyl acetate solution was dried and concentrated in vacuo to give the individual intermediates **3**. The crude acylserines **3** were dissolved in CH_2Cl_2 (3 mL) and returned to fresh reaction vessels on the Quest. The reaction block was cooled to −7 °C, and 1.1 equiv of a 2 M solution of DAST in CH_2Cl_2 was added to each reaction vessel with gentle agitation. After 30 min of agitation, a second portion of 1.1 equiv of the DAST solution was added, and the reaction mixture was allowed to proceed for an additional 30 min. A solution of saturated $NaHCO_3$ was added to quench the reaction, and the block was warmed to ambient temperature. The organic phases were drained, dried over Na_2SO_4, and concentrated in vacuo to give the individual oxazoline methyl esters **4**.

Each ester **4** was dissolved in 1 mL of anhydrous benzene and returned to fresh reaction vessels. To each was added, with gentle agitation, 1.25 equiv of a 1 M benzene solution of dimethyl(*p*-anisyloxyamino)aluminum chloride (prepared from anisyloxyamine HCl and trimethylaluminum according to ref 7b). The reaction block was heated to 50 °C for 5 h, then cooled to ambient temperature. Each reaction vessel was treated with water (100 equiv per mmol of aluminum complex), agitated for 10 min, diluted with ethyl acetate, and filtered through a bed of Celite to remove the aluminum salts. The organic phases were separated, dried over Na_2SO_4, and concentrated in vacuo to give the individual oxazoline carboxylic acid *p*-anisyloxyamides, which were purified by radial chromatography using step gradients of 30-100% ethyl acetate in hexane as eluant. Each was treated with 1.6 mL of 30% TFA in CH_2Cl_2 at ambient temperature for 90 min and concentrated in vacuo, and the residue was triturated with cold diethyl ether to precipitate the hydroxamic acid. Purification of the crude hydroxamic acid was performed on preparative thin-layer chromatography plates (3:97 MeOH/CH_2Cl_2 as eluant).

Method B. To a solution of aromatic acid (1 mmol) in 4 mL of solvent (CH_2Cl_2 with DMF added as required for solubility or DMF alone) was added sequentially serine methyl ester HCl (0.98 mmol), EDCI (1 mmol), HOBt (0.95 mmol), and DIEA (2.25 mmol). The reaction mixture was stirred (or agitated) at room temperature for 16 h. The solution was then diluted with ethyl acetate and washed sequentially with 1 M HCl, saturated sodium bicarbonate, water, and brine. The organic layer was dried over magnesium sulfate and concentrated to give acylserines **3** in yields and purity comparable to those of the product via method A.

Methods C and F (with Partial Racemization at Cα, Oxazoline-C4). Individual carboxylic acids (1.5 mmol) were dispensed into 10 mL reaction vessels and dissolved in CH_2Cl_2 (3 mL). If necessary, THF (1−2 mL) was added for complete dissolution of the acid. The reaction vessels were purged with nitrogen, cooled to 5 °C, and treated with oxalyl chloride (140 μL, 1.60 mmol) and catalyst DMF (5 μL). The reaction vessels were agitated at 5 °C for 30 min, warmed to 20 °C for 1 h, and recooled to 5 °C. A solution (2.0 mL) of D-serine methyl ester hydrochloride (0.79 M) and DIEA (2.2 M) in CH_2Cl_2 was added dropwise to each reaction vessel, and the solutions were agitated at 5 °C for 30 min and then warmed to ambient temperature for 14 h. Each reaction mixture was drained, filtered through silica gel (1 g) eluting with CH_2Cl_2/THF (7:1), and concentrated under a stream of nitrogen to a volume of 5 mL. The crude acylserines **3** were dispensed into fresh reaction vessels, returned to the Quest, and cyclized using the standard DAST procedure. Crude oxazoline methyl esters **4** were dissolved in MeOH (3 mL), cooled to 3 °C, treated sequentially with hydroxylamine hydrochloride (104 mg, 1.5 mmol), and sodium methoxide (1.4 mL, 2.05 M, 2.9 mmol) in MeOH, and agitated at 3 °C for 14 h. Water (2.5 mL) and 1 M HCl (2 mL) were added, and the resulting precipitates were agitated for 20 min. The solutions were drained, leaving the crude hydroxamic acids in the reaction vessels. The hydroxamic acids were washed with H_2O (5 mL) and Et_2O (7 mL), dried under high vacuum, and used without further purification.

Note that the use of oxalyl chloride in the coupling reaction also resulted in introduction of a chlorine at the C-3 position of the indole ring in compound **64**.

2-Aryloxazoline-4-hydroxamic Acids. All solution-phase library compounds were characterized by, at a minimum, proton NMR and mass spectrometry. Purity was determined by reverse-phase HPLC (≥90% unless otherwise indicated) or thin-layer chromatography (single spot in two systems, unless otherwise indicated). Analytical data for selected compounds are given below.

The 2-aryloxazoline-2-hydroxamic acids and *N*-benzoylserine hydroxamic acids produced displayed nearly invariant ^{1}H NMR (500 MHz) data in DMSO-d_6. For the oxazolines the NCHCH$_2$O unit appears as a dd (J = 10, 8.5 Hz) at 4.69 ± 0.03 and an AB pattern centered at 4.54 ± 0.04 (J_{AB} = 9 Hz, $\Delta\delta_{AB}$ = 0.078 ± 0.015 ppm), and the CONHOH function is characterized by singlets at 9.03 ± 0.03 and 10.84 ± 0.04 ppm. In the *N*-benzoylserines, the characterizing pattern for the NCαH−CβH_2OH unit was 4.96 (OH, t), ∼4.42 (Hα, dt, J = 7, 3.5 Hz), and 3.67 ppm (βCH_2, AB of ABX, J_{AB} = 11 Hz) with the CONHOH function signals slightly upfield (10.69 for the NH, 8.84 for the OH) relative to the values for the oxazoline series. These signals are not reported in detail for the compounds listed below when the spectra were recorded in DMSO-d_6 at 11.4 T; when this is the case, the solvent and reference frequency are not listed. The specific methods used for each hydroxamic acid are listed.

4-Methoxy-3-trifluoromethoxyphenyl (20) (methods C and F): mp 165−166 °C; CD $[\theta]_{255}$ = −3300 (30% ee); ^{1}H NMR δ 9.01 (s), 7.87 (H-6, dd, J = 1.5, 8.5), 7.79 (H-2), 7.36 (H-5, d, J = 8.5), 4.67/4.56/4.485 (CHCH$_2$), 3.93 (3H, s); ^{13}C NMR δ 167.05 (CONHOH), 162.77/66.80/69.94 (oxaz-C2,4,5), 162.77 (CONHOH), 154.24 (C4), 136.52 (C3), 128.82 (C6), 122.24 (C2), 120.25 (OCF$_3$, q, ^1J = 256.4), 119.57 (C1), 113.83 (C5), 56.52 (OCH$_3$); ^{19}F NMR δ −59.43; MS, m/z 321.1 (M + H)$^+$, 343.0 (M + Na)$^+$.

4-(3′-Fluorobenzyloxy)-3-trifluoromethoxyphenyl (21) (methods C and F): CD $[\theta]_{257}$ = −4600 (40% ee); ^{1}H NMR δ 10.9 and 9.01 (CONHOH), 7.87 (H-6, dd, J = 1.5, 8.5), 7.82 (H-2, s), 7.47 (H-5′, td, J = 8.2, 5.5), 7.43 (H-5 or -6′, d, J = 8.5), 7.29 (H-6′ or -5, d, J = 8.5), 7.27 (H-2′, ∼d), 7.20 (H-4′, ∼td, J = 9.0, 1.5), 5.33 (2H, s), 4.67/4.57/4.48 (CHCH$_2$); ^{13}C NMR δ 166.11 (CONHOH), 161.81/65.88/69.06 (oxaz-C2,4,5), 161.28 (C3′, d, ^1J = 244.2), 152.12 (C4), 137.93 (C1′, d, ^3J = 6.8), 135.80 (C3), 129.77 (C5′, d, ^3J = 8.4), 127.87 (C6), 122.45 (C6′), 121,70 (C2), 119.33 (OCF$_3$, q, ^1J = 256.8), 119.06 (C1), 114.06 (C2′, d, ^2J = 21.2), 114.03 (C5), 113.16 (C4′, d, ^2J = 22.0), 68.48 (CH$_2$); MS, m/z 415 (M + H)$^+$, 437.0732 (M + Na)$^+$, 437.0737 calcd for $C_{18}H_{14}F_4N_2O_5Na$.

4-(But-3′-enyloxy)-3-trifluoromethoxypheny (22) (methods C and F): mp 124−126 °C; CD $[\theta]_{260}$ = −4320 (35% ee); ^{1}H NMR δ 9.01 (s), 7.85 (H-6, dd, J = 2.0, 8.5), 7.78 (H-2, s), 7.37 (H-5, d, J = 8.5), 5.91−5.83 (1H, m), 5.17 (1H, dd, J = 1.5, 17.0), 5.09 (1H, d, J = 10.5), 4.67/4.56/4.48 (CHCH$_2$), 4.20 (2H, t, J = 6.5), 2.53−2.50 (2H, m); ^{13}C NMR δ 166.12 (CONHOH), 161.84/65.85/68.99 (oxaz-C2,4,5), 152.62 (C4),

135.65 (C3), 133.32 (C3′), 127.86 (C6), 119.29 (OCF_3, q, ^1J = 256.9), 121.56 (C2), 118.55 (C1), 116.40 (C4′), 113.54 (C5), 67.05 (C1′), 31.86 (C2′); ^{19}F NMR δ −59.36; MS, *m/z* 361 (M + H)$^+$, 383.0827 (M + Na)$^+$, 383.0831 calcd for $C_{15}H_{15}F_3N_2O_5$-Na.

3-Trifluoromethoxy-4-allyloxyphenyl ((±)-23) (methods A and F): MS, *m/z* 347 (M + H)$^+$; 400 MHz NMR spectrum was identical with the spectrum of (+)-**23**, prepared for comparison (methods B and E). (+)-**23**: ^{1}H NMR δ 10.83 and 9.01 (CONHOH), 7.855 (H-6, dd, *J* = 2, 8.5), 7.80 (H-2, s), 7.355 (H-5, d, *J* = 8.5), 6.045 (=CH, m), 5.42 (=CH_2, 1H, dd, *J* = 17, 1), 5.34 (=CH_2, 1H, dd, *J* = 10, 1), 4.765 ($OCH_{2'}$, d, *J* = 5), 4.67/4.57/4.49 (CH$\alpha$$CH_2\beta$); MS, *m/z* 346.9 (M + H)$^+$. The *S* enantiomer displayed a positive CD extremum ($[\theta]_{258}$ = +16 100) in analogy to (+)-**5** (the *S* isomer of **5**) and an IC_{50} of 13 μM (versus 0.12 μM for (±)-**23**).

3-Trifluoromethoxy-4-prenyloxyphenyl ((±)-24) (methods A/F): ^{1}H NMR δ 10.8 and 9.02 (CONHOH), 7.86 (H-6, dd, *J* = 2, 8.5), 7.78 (H-2, s), 7.34 (H-5, d, *J* = 8.5), 5.46 (=CH, t, *J* = 6.5), 4.73 ($OCH_{2'}$, d, *J* = 6), 4.67/4.57/4.49 (CH$\alpha$$CH_2\beta$), 1.80 (3H, s), 1.76 (3H, s); MS, *m/z* 375 (M + H)$^+$.

3-Chloro-4-trifluoromethoxyphenyl (27) (methods C and F): ^{1}H NMR δ 9.034 (CONHO*H*, d, *J* = 1), 8.135 (H-2, d, *J* = 2), 7.96 (H-6, dd, *J* = 8, 2), 7.715 (H-5, dq, *J* = 8, 1), 4.736 (dd, *J* = 10.3, 7.7), 4.622 (~t), 4.529 (~t); ^{13}C NMR δ 166.77 (CONHOH), 162.11/66.77/67.0/70.42 (oxaz-C2,4,5), 146.29 (C4), 130.46 (C2), 128.76 (C6), 127.55 (C3), 126.30 (C1), 123.16 (C5), 119.95 (OCF_3, q, ^1J = 258.9); ^{19}F NMR δ −58.72; MS, *m/z* 325.0 and 327.0 (M + H)$^+$, 346.9 and 349.0 (M + Na)$^+$.

4-Butylphenyl (29) (methods A and E): ^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD) δ 7.85 (2H, d, *J* = 8.1), 7.26 (2H, d, *J* = 8.1), 4.79 (1H, t, *J* = 9.0), 4.64 (2H, q, *J* = 8.6), 2.67 (2H, t, *J* = 7.6), 1.66−1.58 (2H, m), 1.39−1.34 (2H, m), 0.94 (3H, t, *J* = 7.3); MS, *m/z* 263.1 (M + H)$^+$.

4-(Hept-1-yloxy)phenyl (30) (methods A/E): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.7), 6.93 (2H, d, *J* = 8.7), 4.81 (1H, dd, *J* = 9.5, 8.9), 4.69−4.64 (2H, m), 4.02 (2H, t, *J* = 6.4), 1.82−1.77 (2H, m), 1.48−1.43 (2H, m), 1.39−1.31 (6H, m), 0.90 (3H, t, *J* = 6.4); MS, *m/z* 321.1 (M + H)$^+$.

4-(But-3-enyloxy)phenyl (31) (methods A and D): ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (2H, d, *J* = 8.6), 6.96 (2H, d, *J* = 8.6), 5.97−5.86 (1H, m), 5.17 (1H, dd, *J* = 18.8, 1.6), 5.10 (1H, dd, *J* = 10.3, 1.4), 4.80−4.56 (3H, m), 4.09 (2H, t, *J* = 6.6), 2.56 (2H, q, *J* = 5.0); MS, *m/z* 277.0 (M + H)$^+$.

4′-Propylbiphen-4-yl (32) (methods A and E): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (1H, s), 9.03 (1H, s), 7.95 (2H, d, *J* = 8.4), 7.78 (2H, d, *J* = 8.4), 7.65 (2H, d, *J* = 8.2), 7.31 (2H, d, *J* = 8.2), 4.69 (1H, dd, *J* = 9.9, 7.8), 4.60−4.48 (2H, m), 2.60 (2H, t, *J* = 7.4), 1.67−1.58 (2H, m), 0.92 (3H, t, *J* = 7.3); MS, *m/z* 325.1 (M + H)$^+$.

4-(3′-Nitrobenzyloxy)phenyl (33) (methods B and F): mp 178−179 °C; ^{1}H NMR δ 10.81 and 9.00 (CONHOH), 8.34 (H-2′, s), 8.22 (H-4′, dd, *J* = 1.5, 8.0), 7.93 (H-6′, d, *J* = 8.0), 7.85 (H-2,6, d, *J* = 8.5), 7.72 (H-5′, t, *J* = 8.0), 7.15 (H-3,5, d, *J* = 8.5), 5.35 (2H, s), 4.64/4.53/4.46 ($CHCH_2$); MS, *m/z* 358.0 (M + H)$^+$.

4-(3′-Nitrophenoxymethyl)phenyl (34) (methods C and F): ^{1}H NMR δ 9.02 (CONHO*H*), 7.92 (H-2,6, d, *J* = 8), 7.85−7.77 (H-2′,4′, overlapped), 7.59 (H-3,5, d, *J* = 8) overlapped with 7.60 (H-5′, t), 7.51 (H-6′, dt), 5.34 (2H, s), 4.68/4.57/4.49 ($CHCH_2$); MS, *m/z* 358 (M + H)$^+$, 380 (M + Na)$^+$.

4-Fluorophenyl (35) (methods B and D): $[\alpha]^{25}_D$ −68.9° (*c* 0.16, CH_3OH); CD $[\theta]_{244}$ = −20 200; ^{1}H NMR (400 MHz, CD_3-OD) δ 7.85 (H-3,5, dd, *J* = 8. 5), 7.05 (H-2,6, ~t), 4.9−5.0 (Hα, m), 4.5−4.9 ($CH_2\beta$, AB of ABX); ^{13}C NMR (100 MHz, CD_3OD) δ 167.07 (CONHOH), 163.26/66.85/69.84 (oxaz-C2,4,5), 164.19 (C4, d, ^1J = 249.6), 130.70 (C2,6, d, ^3J = 9.3), 123.57 (C1, d, ^4J = 2.8), 115.83 (C3,5, d, ^2J = 22.0); ^{19}F NMR δ −107.57; MS, *m/z* 225.0675 (M + H)$^+$, calcd for $C_{10}H_{10}FN_2O_3$ 225.0674. Anal. found C 52.98, H 3.69, N 12.16; calcd for $C_{10}H_9FN_2O_3$, C 53.57, H 4.05, N 12.50.

4-Fluoro-3-trifluoromethylphenyl (36) (methods C and F): mp 169−171°C; ^{1}H NMR δ 9.03 (OH, s), 8.23−8.21 (H-2,6, m), 7.68 (H-5, ~t, *J* = 10), 4.74/4.63/4.54 ($CHCH_2$); ^{13}C NMR δ 166.83 (CONHOH), 162.20/66.99/70.46 (oxaz-C2,4,5), 160.74 (C4, d, ^1J = 258.9), 135.03 (C6, d, ^3J = 10.1), 127.11 (C2), 124.06 (C1), 122.19 (CF_3, q, ^1J = 272.7), 118.15 (C5, d, ^2J = 21.4), 117.15 (C3, dq, J_{C3-CF3} = 32.7, J_{C3-CF} = 13.8); ^{19}F NMR δ −62.65 (CF_3), −109.99 (F); MS, *m/z* 293.0 (M + H)$^+$.

4-Fluoro-3-methylphenyl (37) (methods C and F): mp 169−171°C; ^{1}H NMR δ 9.01 (OH, s), 7.84 (H-2, bd, *J* = 6.5), 7.74 (H-6, ddd), 7.25 (H-5, ~t, *J* = 9.5), 4.66/4.55/4.48 ($CHCH_2$), 2.28 (3H, s); ^{13}C NMR δ 167.08 (CONHOH), 163.36/66.82/69.73 (oxaz-C2,4,5), 163.36 (CONHOH), 162.74 (C4, d, ^1J = 247.6), 131.70, (C2, d, ^3J = 5.0), 127.97 (C6, d, ^3J = 8.8), 124.92 (C3, d, ^2J = 17.6), 123.23 (C1), 115.40 (C5, d, ^2J = 22.6), 14.07 (CH_3); ^{19}F NMR δ −111.70; MS, *m/z* 221, 239.0 (M + H)$^+$, 261.0 (M + Na)$^+$.

Racemic 3-Fluoro-4-allyloxyphenyl (39) (methods A and F): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (1H, s), 9.02 (1H, s), 7.85 (1H, dd, *J* = 8.7, 2.1), 7.80 (1H, s), 7.35 (1H, d, *J* = 8.8), 6.08−6.01 (1H, m), 5.42 (1H, dd, *J* = 17.24, 1.7), 5.31 (1H, dd, *J* = 10.6, 1.6), 4.77−4.46 (5H, m); MS, *m/z* 346.8 (M + H)$^+$.

4-(3′-Trifluoromethylbenzyloxy)-3-fluorophenyl (40) (methods B and F): mp 173−175 °C; ^{1}H NMR δ 10.81 and 9.01 (CONHOH), 7.85 (H-2′, s), 7.79 and 7.74 (H-6, H-4′, d's), 7.68−7.71 (2H, m), 7.39 (H-5, t), 5.37 (CH_2, s), 4.66/4.55/4.47 ($CHCH_2$); MS, *m/z* 398.8 (M + H)$^+$, 420.7 (M + Na)$^+$, 397.5 (M$^•$)$^+$, and 795.5 (dimer, M$^•$)$^+$.

4-(2′-Trifluoromethoxybenzyloxy)-3-fluorophenyl (41) (methods A and F): mp >200°C; ^{1}H NMR δ 10.81 and 9.01 (CONHOH), 7.73−7.68 (H-2, 6, 6′, m), 7.55 (1H, ~t), 7.50−7.42 (3H, m), 5.30 (CH_2, s), 4.67/4.56/4.47 ($CHCH_2$); MS, *m/z*. 415.0 (M + H)$^+$, 437.0 (M + Na)$^+$.

5-Bromo-4-methoxy-3-fluorophenyl (42) (methods B/F): mp 178−180°C; ^{1}H NMR δ 10.81 and 9.02 (CONHOH), 7.92 (H-6, s), 7.74 (H-2, d, *J* = 11.4), 4.70/4.59/4.50 ($CHCH_2$), 3.97 (3H, s); MS, *m/z* 333.0 and 335.0 (M + H)$^+$, 331 and 333 (M − H)$^-$.

3-Fluoro-4-methoxy-5-allyl-6-methylphenyl (43) (methods C and F): ^{1}H NMR δ 9.01 (CONHO*H*), 7.462 (H-2, s), 5.90 (=CH, m), 5.01 (=CH_2, 1H, dd, *J* = 10, 1), 4.84 (=CH_2, 1H, dd, *J* = 17, 1), 4.69/4.50/4.41 ($CHCH_2$), 3.865 (3H, d, *J* = 1), 3.45 (CH_2, d, *J* = 5.5), 2.39, (Me, s); MS, *m/z*. 309.1 (M + H)$^+$, 331.1 (M + Na)$^+$.

4-Fluoro-3-bromophenyl (45) (methods C and F): mp 171−172 °C; ^{1}H NMR δ 9.02 (d, *J* = 1.0), 8.18 (H-2, dd, *J* = 2.0, 6.5), 7.92 (H-6, ddd, *J* = 2.0, 5.0, 8.5), 7.52 (H-5, ~t, *J* = 8.5), 4.71/4.595/4.505 ($CHCH_2$); MS, *m/z* 285, 287, 303.0, and 304.9 (M + H)$^+$, 325.0 and 327.0 (M + Na)$^+$.

5-Fluoro-3-trifluoromethylphenyl (46) (methods C and F): mp 164−166°C; ^{1}H NMR δ 9.05 (s), 8.025 (H-2, s), 7.98 (H-4, d, *J* = 8.0), 7.96 (H-6, d, *J* = 9.0), 4.775/4.66/4.56 ($CHCH_2$); MS, *m/z* 275, 293.0 (M + H)$^+$.

3-Trifluoromethylphenyl (47) (methods A and E): ^{1}H NMR (400 MHz, Me_2CO-d_6) δ 8.47 (H_{Ar}, s), 8.42 (H_{Ar}, d, *J* = 8.1), 8.11 (H_{Ar}, d, *J* = 7.6), 7.96 (H_{Ar}, t, *J* = 8.0), 5.08−5.1 (Cα, m), 4.85−4.91 ($CH_2\beta$, AB of ABX); MS, *m/z* 275.0 (M + H)$^+$.

3-Trifluoromethyl-4-allyloxyphenyl (48) (methods C and F): ^{1}H NMR δ 8.94 (1H, d), 8.10 (H-2,6, m), 7.38 (H-5, d, *J* = 9.5), 6.04 (1H, m), 5.43 (1H, dd, *J* = 17.5, 1.5), 5.30 (1H, dd, *J* = 9, 1.5), 4.81 (CH_2, s), 4.69/4.59/4.50 ($CHCH_2$); MS, *m/z* 331.1 (M + H)$^+$, 353.1 (M + Na)$^+$.

4-Trifluoromethylphenyl (49) (methods C and F): mp 194−195 °C; ^{1}H NMR δ 9.04 (OH, d, *J* = 1.5), 8.09 (H-3,5, d, *J* = 8.0), 7.88 (H-2,6, d, *J* = 8.0), 4.735/4.62/4.54 ($CHCH_2$); ^{13}C NMR δ 166.81 (CONHOH), 163.07/66.96/70.07 (oxaz-C2,4,5), 163.07 (CONHOH), 131.62 (C4, q, ^2J = 31.4), 130.76 (C1), 128.92 (C2,6), 125.69 (C3,5), 123.88 (CF_3, q, ^1J = 271.5); ^{19}F NMR δ −63.92; MS, *m/z* 275.0 (M + H)$^+$, 297.0 (M + Na)$^+$.

6-Trifluoromethylpyrid-3-yl (50) (methods C and F): ^{1}H NMR δ 10.9 and 9.07 (CONHOH), 9.21 (H-2, bs), 8.50 (H-5, d), 8.06 (H-4, d, *J* = 8.0), 4.78/4.66/4.57 ($CHCH_2$); MS, *m/z* 276.0 (M + H)$^+$, 298.0 (M + Na)$^+$.

Racemic 4-Nitrophenyl (51) (methods A and F): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (NH, s), 9.07 (OH, s), 8.34 (2H, d, *J* = 9.0), 8.14 (2H, d, *J* = 9.0), 4.76 (1H, dd, *J* = 10.0,

7.8), 4.63 (1H, dd, J = 10.0, 8.2), 4.56 (1H, dd, J = 8.2, 7.8); MS, m/z 251.9 $(M + H)^+$.

4-Dimethylaminophenyl (52) (methods A and F): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, J = 9.0), 6.85(2H, d, J = 9.0), 4.69/4.59/4.50 ($CHCH_2$), 3.00 (6H, s, $N(CH_3)_2$); MS, m/z 250.0 $(M + H)^+$.

4-Hydroxyphenyl (53) (methods A and F): ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 7.81 (2H, d, J = 8.8), 6.85 (2H, d, J = 8.8), 4.75 (1H, dd, J = 10.1, 8.1), 4.61−4.56 (2H, m); MS, m/z 223.0 $(M + H)^+$.

Racemic 4-Bromophenyl (54) (methods A and F): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (1H, s), 9.02 (1H, s), 7.81, (2H, d, J = 8.6), 7.71 (2H, d, J = 8.6), 4.68 (1H, dd, J = 9.9, 7.7), 4.57 (1H, dd, J = 9.9, 8.0), 4.49 (1H, dd, J = 8.0, 7.7); MS, m/z 284.8 $(M + H)^+$.

Racemic 4-Iodophenyl (55) (methods A and F): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (1H, d, J = 1.5), 9.02 (1H, d, J = 1.5), 7.88 (2H, d, J = 8.5), 7.65 (2H, d, J = 8.5), 4.67 (1H, dd, J 9.9, 7.7), 4.56 (1H, dd, J = 9.9, 8.1), 4.48 (1H, dd, J = 8.1, 7.7); MS, m/z 332.8 $(M + H)^+$.

4-Acetylphenyl (56) (methods A and F): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (1H, s), 9.05 (1H, s), 8.06 (2H, d, J = 8.6), 8.01 (2H, d, J = 8.6), 4.72 (1H, dd, J = 10.0, 7.9), 4.60 (1H, dd, J = 10.0, 8.2), 4.53 (1H, dd, J = 8.2, 7.9), 2.62 (3H, s); MS, m/z 249.0 $(M + H)^+$.

4-Acetamidopheny (57) (methods A and F): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (1H, d, J = 1.4), 10.21 (1H, s), 9.00 (1H, d, J = 1.4), 7.81 (2H, d, J = 8.7), 7.68 (2H, d, J = 8.7), 4.63 (1H, dd, J = 9.9, 7.8), 4.52 (1H, dd, J = 9.9, 7.8), 4.45 (1H, dd, J = 8.1, 7.8), 2.01 (3H, s); MS, m/z 264.0 $(M + H)^+$.

4,5-Benz-(1*H*)-pyrazol-3-yl (60) (methods A and D): ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (1H, d, J = 8.2), 7.60 (1H, d, J = 8.5), 7.45 (1H, t, J = 7.2), 7.28 (1H, t, J = 7.6), 4.92−4.81 (1H, m), 4.75−4.65 (2H, m); MS, m/z 246.9 $(M + H)^+$.

1-Butyl-4,5-benz-(1*H*)-pyrazol-3-yl (61) (methods A and E): ^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD) δ 8.16 (1H, d, J = 8.2), 7.50−7.43 (2H, m), 7.30 (1H, dt J = 7.6, 1.3), 4.97 (1H, dd, J = 10.3, 8.6), 4.73 (2H, q, J = 8.8), 4.46 (2H, t, J = 7.1), 1.94 (2H, q, J = 7.4), 1.38−1.30 (2H, m), 0.94 (3H, t, J = 7.3); MS, m/z 303.1 $(M + H)^+$.

1-Butyl-3,4-benz-(1*H*)-pyrazol-5-yl (62): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (1H, s), 9.06 (1H, s), 8.18 (1H, d, J = 8.2), 7.80 (1H, d, J = 8.6), 7.48 (1H, t, J = 7.2), 7.29 (1H, t, J = 7.5), 4.75 (1H, dd, J = 9.9, 7.8), 4.56 (1H, dd, J = 9.7, 8.1), 4.51−4.47 (3H, m), 1.87−1.80 (2H, m), 1.26−1.20 (2H, m), 0.88 (3H, t, J = 7.4); MS, m/z 303.1 $(M + H)^+$.

Racemic 5-Fluoroindol-2-yl (63) (methods A and F): ^{1}H NMR δ 10.80 and 9.10 (CONHOH), 7.37−7.40 (2H, m), 7.07−7.08(1H, m), 6.95 (1H, s), 4.49−4.70 (3H, m); MS, m/z 264.0703 $(M + H)^+$, calcd for $C_{12}H_{11}FN_3O_3$, 264.0785.

5-Fluoro-2-chloroindol-2-yl (64) (methods C and F): ^{1}H NMR δ 10.90 and 9.10 (CONHOH), 7.47 (H-7, dd, J = 4.5, 9.0), 7.32 (H-4, dd, J = 2.0, 9.0), 7.19 (H-6, dt, J = 2.5, 9.0), 4.71/4.62/4.53 ($CHCH_2$); MS, m/z 298.00 and 299.99 $(M + H)^+$, 320.03 and 322.01 $(M + Na)^+$.

General Procedures for the Solution-Phase Parallel Synthesis of *N*-Acylserine Hydroxamic Acids. Method F. *N*-Benzoyl-D-serine methyl ester **3** (0.4 mmol, in 4 mL MeOH) from methods A, B, or C was added to an ice-cold solution of hydroxylamine hydrochloride (0.42 mmol) in methanol (2 mL) to which 80 μL of 25% methanolic NaOMe had been added. An additional 60 μL portion of methoxide solution was added, and the resulting cloudy solution was stirred for 4−10 h at 0 °C. The reaction mixture was then diluted with water (3 mL) and washed with CH_2Cl_2 (5 mL). The aqueous layer was cooled to 0 °C and acidified (1 N HCl) to pH 2. At this point, the desired hydroxamic acid precipitated out and was collected by filtering the thick suspension. If no, or a modest quantity of, precipitate formed, the hydroxamic acid was obtained by $CHCl_3$ extraction. In either case, the resulting solid was washed with a limited amount of water and several portions of ether to give a white solid.

Method G. To a solution of *N*-benzoyl-D-serine methyl ester **3** (0.40 mmol) in methanol (2 mL) was added a solution of lithium hydroxide (50 mg, 3 equiv) in water (1 mL). After being stirred for 12 h at room temperature, the mixture was diluted with water (5 mL), the aqueous mixture was washed with CH_2Cl_2 (2 × 5 mL), and the acid (typically a white solid) was isolated by extraction with $CHCl_3$ (2 × 10 mL) after acidification with 1 N HCl. The entire acid sample, in 3 mL of DMF, was treated sequentially with 60 mg of *O*-benzylhydroxylamine·HCl (0.37 mmol), 80 mg of EDCI (0.41 mmol), 60 mg of HOAt (0.40 mmol), and 0.15 mL of DIEA (0.86 mmol) and was then stirred for 16 h at room temperature. The resulting solution was diluted with 15 mL of EtOAc, washed with 1 N HCl (3 × 3 mL), saturated aqueous $NaHCO_3$ (3 × 3 mL), water, and brine. The benzyloxyamide obtained by evaporating the dried solution was hydrogenated at 1 atm in 5 mL of EtOH over 50 mg of 20% $Pd(OH)_2$ for 6−16 h. Filtration of the catalyst followed by concentration in vacuo afforded a residue that crystallized upon trituration with ether (overall yield, 45−65%). The following *N*-benzoylserine hydroxamates are representative.

4-Fluoro (67) (methods B and F): mp 178−180 °C; CD $[\theta]_{237}$ = −4500; ^{1}H NMR δ 10.71 and 8.82 (CONHOH), 8.32 (NH, d, J = 7.7), 7.98 (H-2,6, dd, J = 7.8, 5.7), 7.30 (H-3,5, dd, J = 7.8, 9.2), 4.96 (OH, t, J = 5.6), 4.42 (H, ∼q, J = 6.4), 3.68 (2H, AB of ABX); MS, m/z 243.0 $(M + H)^+$, 265.0 $(M + Na)^+$.

4-Fluoro-3-ethoxy (68) (methods A and F): mp 152−153 °C; ^{1}H NMR δ 10.68 and 8.84 (CONHOH), 8.35 (NH, d, J = 8.0), 7.66 (H-2, dd, J = 2.0, 8.5), 7.51 (H-6, ddd, J = 2.0, 4.5, 8.5), 7.30 (H-5, dd, J = 8.5, 11.0), 4.96 (OH, t, J = 5.8), 4.42 (Hα, q, J = 6.5), 4.18 (2H, q, J = 7.0), 3.67 (βCH_2, AB of ABX), 1.38 (3H, t, J = 7.0); MS, m/z 309.0858 $(M + Na)^+$, calcd for $C_{12}H_{15}FN_2O_5Na$, 309.0863.

4-Trifluoromethoxy (69) (methods C and F): mp 161−162 °C; CD $[\theta]_{238}$ = −2600; ^{1}H NMR δ 10.73 and 8.84 CONHOH), 8.43 (NH, d), 8.02 (H-2,6, d, J = 8), 7.49 (H-3,5, d, J = 8), 4.96 (OH, t), 4.42 (1Hα, ∼q), 3.68 (2H, AB of ABX); MS, m/z − 276.0 $(M - NHOH)^+$, 309.0692 $(M + H)^+$, calcd $C_{10}H_{12}F_3N_2O_5$, 309.0698, 331.0518, calcd $C_{10}H_{11}F_3N_2O_5Na$, 331.0518.

3-Trifluoromethoxy-4-allyloxy (70) (methods A and F): mp 123−124 °C; CD $[\theta]_{249}$ = −7500; ^{1}H NMR δ 10.68 and 8.83 (CONHOH), 8.38 (NH, d, 8.0), 7.94 (H-6, d, J = 8.5), 7.92 (H-2, s), 7.32 (H-5, d, J = 8.5), 6.04 (1H, m), 5.42 (1H, dd, J = 1.5, 17.5), 5.30 (1H, d, J = 11.0), 4.94 (OH, t, J = 5.8), 4.75 (2H, d, J = 4.5), 4.41 (Hα, q, J = 7.0), ∼3.66 (βCH_2, AB of ABX); MS, m/z 365 $(M + H)^+$, 387 $(M + Na)^+$.

3-Trifluoromethoxy-4-methoxy-5-propyl (71) (methods C and G): mp 139−141 °C; CD $[\theta]_{245}$ = −6350; ^{1}H NMR δ 10.69 and 8.85 (CONHOH), 8.45 (NH, d, 7.7), 7.84 and 7.76 (H6,-2), 4.96 (OH, t, 5.6), 4.42 (Hα, ∼q, ∼6.4), 3.84(3H, s), 3.67 (βCH_2, AB of ABX), 2.64 (CH_2, ∼t), 1.61 (CH_2, ∼sextet), 0.94 (CH_3, t); MS, m/z 381.0 $(M + H)^+$, 403.1 $(M + Na)^+$.

Synthesis of Oxazine Hydroxamic Acids. *O*-*tert*-Butyldimethylsilyl-DL-homoserine Methyl Ester 15. To a solution of *tert*-butylmethylsilyl chloride (21.5 g, 143 mmol) and DBU (20.5 mL, 137 mmol) in acetonitrile (40 mL) was added DL-homoserine (4.9 g, 41 mmol) in portions over 30 min. The solvent was removed in vacuo, and the residue was extracted into diethyl ether, washed with water, and allowed to stand. A white precipitate formed and was filtered to give the silyl ether in a state suitable for the next reaction (5.3 g, 22.6 mmol, 55%): ^{1}H NMR (400 MHz, CD_3OD) δ 4.8 (NH_2, s), 3.8 (OCH_2, t), 3.6 (Hα, m), 2.1−1.8 ($CH_{2'}$, m), 0.8 ($C(CH_3)_3$, s), 0.1 ($Si(CH_3)_2$, s); ^{13}C NMR (100.6 MHz, CD_3OD) δ 173.88 (COOH), 62.05 (OCH_2), 54.92 (CH), 34.36 (CH_2), 26.40 ($(CH_3)_3$), 19.10 ($SiC(CH_3)_3$), −5.39 ($(CH_3)_2Si$); MS (APCI$^+$), m/z 234 $(M + H)^+$.

To a solution of *O*-*tert*-butyldimethylsilyl-DL-homoserine (250 mg, 1.1 mmol) in methanol (3 mL) and benzene (10.5 mL) was added trimethylsilyldiazomethane (2.7 mL, 5.4 mmol). The mixture was stirred at ambient temperature overnight. The solvents were removed in vacuo to give the methyl ester (280 mg, 1.1 mmol, 100%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.8−3.7

(OCH_2, m), 3.7 (OCH_3, s), 3.6−3.55 (CH, m), 2.0−1.9 (0.5 CH_2, m), 1.8 (NH_2, s), 1.7−1.65 (0.5 CH_2, m), 0.8 ($C(CH_3)_3$, s), 0.1 ($Si(CH_3)_2$, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.95 ($COOCH_3$), 59.83 (OCH_2), 51.90 (CH), 36.57 (CH_2), 25.80 (($CH_3)_3$), 18.17 ($SiC(CH_3)_3$); MS (APCI$^+$), *m/z* 248 $(M + H)^+$.

General Procedure for the Preparation of 2-Aryl-4,5-dihydrooxazine-4-carboxylic Acid Hydroxamides 73−75. Substituted benzoic acid (1.2 mmol), *O*-*tert*-butyldimethylsilyl-DL-homoserine methyl ester (1 mmol), HATU (1.2 mmol), HOAt (1.2 mmol), and DIEA (2.5 mmol) were dissolved in dry DMF (5 mL). The resulting yellow-orange solution was stirred at ambient temperature under N_2 overnight. Ethyl acetate (15 mL) and water (10 mL) were added to the reaction mixture. The organic layer was separated and washed with saturated $NaHCO_3$ solution (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil. The crude products were purified on a silica gel flash column (47−73% yield, 5:6 EtOAc/hexanes as eluant).

To each of the resulting amides (0.5 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added DAST (2 mmol), and the reaction mixtures were stirred at ambient temperature under N_2 for 4 h. Saturated $NaHCO_3$ solution was added, and the products were extracted into CH_2Cl_2 (2 mL). In all cases, the organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo to give the crude products as yellow oils that were purified on a silica gel flash column (35:65 EtOAc/hexanes as eluant), affording the oxazine methyl esters **17** (54−77% yield).

To a 0 °C solution of hydroxylamine hydrochloride (0.3 mmol) in dry methanol (1 mL) was added sodium methoxide (25% methanolic solution, 1.5 mmol), and the solution was stirred at 0 °C under N_2. A solution of each oxazine methyl ester **17** (0.3 mmol) in methanol (1 mL) was cooled at 0 °C and added via syringe to the hydroxylamine solution. The mixture was stirred at 0−5 °C under N_2 overnight, then acidified to pH 4.0 with dilute HCl. The precipitated products were collected by filtration and dried under vacuum. The structure of each oxazine was determined by proton NMR and mass spectrometry, and purity was ≥90% by reverse-phase HPLC.

2-(4-Methylphenyl)-4,5-dihydrooxazine-4-carboxylic acid hydroxamide (73): (24% yield for the last step) ^1H NMR (400 MHz, $CDCl_3$) δ 7.9 (Ar−H, d), 7.2 (Ar−H, d), 4.4−4.6 (CH_2, m), 4.3−4.2 (CH, m), 2.4 (CH_3, s), 2.0−2.3 (CH_2, m); ^{13}C NMR (100.6 MHz, CD_3OD) δ 171.66 (CONHOH), 158.87/55.12/25.65/65.42 (oxaz-C2,4,5,6), 142.50 (C4), 131.88 (C1), 129.72 (C3,5), 128.46 (C2,6), 21.42 (CH_3); MS, *m/z* 235.1082 $(M + H)^+$ (calcd 235.1083), 257.0903 $(M + Na)^+$ (calcd 257.0902).

2-(3-Trifluoromethyl-4-fluorophenyl)-4,5-dihydrooxazine-4-carboxylic acid hydroxamide (74): (18% yield for the last step) ^1H NMR (400 MHz, DMSO-d_6) δ 10.7 and 8.9 (CONHOH), 8.3 (Ar−H, m), 7.6 (Ar−H, t), 4.6−4.4 (CH_2, m), 4.2−4.1 (CH, m), 2.2−1.9 (CH_2, m); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 167.81 (CONHOH), 160.25 (C4, d, ^1J = 257.6), 152.65/53.27/23.93/64.47 (oxaz-C2,4,5,6), 133.96 (C6, d, ^3J = 10.1), 130.18 (C2, d, ^3J = 3.0), 126.11 (C1), 122.49 (CF_3, q, ^1J = 272.7), 117.25 (C5, d, ^3J = 21.1), 116.47 (C3, dq); MS (APCI$^+$), *m/z* 307.0683 $(M + H)^+$ (calcd 307.0706).

2-(5-Fluoroindol-2-yl)-4,5-dihydrooxazine-4-carboxylic acid hydroxamide (75): (12% yield for the last step) ^1H NMR (400 MHz, DMSO-d_6) δ 10.6 and 9.0 (CONHOH), 7.4 (Ar−H, m), 7.3 (Ar−H, d), 7.0 (Ar−H, t), 6.8 (Ar−H, s), 4.2−4.3 (CH_2, m), 4.15−4.10 (CH, m), 2.2−1.7 (CH_2, m); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 167.67 (CONHOH), 157.04 (C5, d, ^1J = 232.4), 150.09/53.11/ 24.46/64.72 (oxaz-C2,4,5,6), 133.31 (C7a), 133.0 (C2), 127.41 (C3a, d, ^3J = 11.1), 112.76 (C7, d, ^3J = 10.1), 111.77 (C6, d, ^2J = 26.2), 105.62 (C4, d, ^2J = 23.1), 102.73 (C3); MS (APCI$^+$), *m/z* 278.1005 (M + H) (calcd 278.0941).

General Procedure for the Synthesis of Thiazoline Hydroxamic Acids. Oxazoline methyl esters **4** were dissolved in 2:1 MeOH/NEt_3 (15 mL/mmol), and the solution was saturated with H_2S gas, then stirred (single synthesis) or agitated (Quest parallel synthesis) at ambient temperature in a closed system for 48 h, repeating the H_2S treatment at 24 h. The volatiles were removed in vacuo, and the residue was dissolved in anhydrous CH_2Cl_2 (5 mL/mmol) and cooled to −10 °C. A freshly prepared 2 M solution of DAST in CH_2Cl_2 (1.1 equiv) was added, and the reaction mixture was stirred or agitated for 90 min at −10 °C, with a second 1.1 equiv of the DAST solution being added at 45 min. The reaction was quenched by addition of excess saturated aqueous $NaHCO_3$, and the mixture was stirred or agitated for 30 min while warming to ambient temperature. The organic phase was separated and dried over Na_2SO_4, and the volatiles were removed in vacuo to give the crude thiazoline methyl esters **18**. The hydroxamic acids were prepared by direct conversion of the methyl esters according to method E or F. The structure of each thiazoline was determined by proton NMR and mass spectrometry, and purity was ≥90% by reverse-phase HPLC.

2-*p*-Tolyl-4,5-dihydrothiazole-4-carboxylic acid hydroxamide (76): ^1H NMR (400 MHz, CD_3OD) δ 7.55 (H-2,6, d, *J* = 8.1), 6.99 (H-3,5, d, *J* = 8.1), 5.15 (Hα, t, *J* = 9.4) 3.40 (CβH_2, AB of ABX), 2.40 (CH_3, s); ^{13}C NMR (100 MHz, CD_3OD) δ 173.60 (CONHOH), 170.31/78.93/36.15 (thiaz-C2,4,5), 143.76 (C4), 131.35 (C1), 130.29 (C3,5), 129.60 (C2,6), 21.48 (CH_3); MS, *m/z* 236.9 $(M + H)^+$. Mass calcd for $C_{11}H_{13}N_2O_2S$, 237.0698; found 237.0751.

2-(4-But-3′-enyloxyphenyl)-4,5-dihydrothiazole-4-carboxylic acid hydroxamide (77): ^1H NMR (400 MHz, CD_3OD) δ 7.90 (H-2,6, d, *J* = 7.7), 7.05 (H-3,5, d, *J* = 8.8), 5.99 (=CH, m), 5.03−5.27 (CH_2=, m over Hα, m), 4.17 (OCH_2, t, *J* = 6.6), 3.64−3.77 (CβH_2, AB of ABX), 2.60−2.63 (CH_2, m); MS, *m/z*. 293.0 $(M + H)^+$.

2-(4-Fluorophenyl)-4,5-dihydrothiazole-4-carboxylic acid hydroxamide (78): ^1H NMR (400 MHz, DMSO-d_6) δ 7.90 (H-3,5, dd, *J* = 5.5, 6.0), 7.34 (H-2,6, t, *J* = 8.9), 5.10 (Hα, t, *J* = 9.08), 3.58−3.71 (CβH_2, AB of ABX); ^{13}C NMR (100 MHz, DMSO) δ 166.87 (CONHOH), 166.62/77.54/35.13 (thiaz-C2,4,5), 164.04 (C4, d, ^1J = 249.8), 130.80 (C2,6, d, *J* = 9.0), 128.95 (C1), 115.85 (C3,5, d, *J* = 22.0); HPLC t_R 33.43 (97.9%); MS, *m/z* 241.2 $(M + H)^+$; HPLC t_R 33.43 (97.9%). Mass calcd for $C_{10}H_{10}N_2O_2FS$, 241.0447; found 241.0471

2-(4-Trifluoromethoxyphenyl)-4,5-dihydrothiazole-4-carboxylic acid hydroxamide (79): ^1H NMR (400 MHz, DMSO-d_6) δ 10.81 and 9.06 (CONHOH), 7.97 (H-3, 5, d, *J* = 8.8), 7.49 (H-2,6, d, *J* = 8.0), 5.14 (Hα, dd, *J* = 9.0, 9.2), 3.65 (CβH_2, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.82 (CONHOH), 166.51/77.61/35.22 (thiaz-C2,4,5), 150.48 (C4), 131.37 (C1), 130.47 (C2,6), 121.09 (C3,5); MS, *m/z* 307.04 $(M + H)^+$; HPLC t_R 37.76 (97.9%). Mass calcd for $C_{11}H_{10}N_2O_3F_3S$, 307.0364; found 307.0350.

2-(4-Methoxy-5-propyl-3-trifluoromethoxyphenyl)-4,5-dihydrothiazole-4-carboxylic acid hydroxamide (80): ^1H NMR (400 MHz, CD_3OD) δ 7.52−7.60 (H-2,6, m), 5.18 (Hα, m), 3.79 (OCH_3, s), 3.73−3.78 (CβH_2, AB of ABX), 2.64−2.80 ($ArCH_2$, m,), 1.23−1.28 (CH_2, m), 0.98 (CH_3, t); MS, *m/z* 379 $(M + H)^+$.

2-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydrothiazole-4-carboxylic acid hydroxamide (81): ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.89 (ArH, m), 5.18 (Hα, m), 3.60−3.79 (CβH_2, AB of ABX), 2.61 (CH_3, s); MS, *m/z*. 303.0 $(M + H)^+$. Mass calcd for $C_{11}H_{10}N_2O_3F_3S$, 307.0364; found 307.0350.

Preparation of [^{3}H-CH_3CONH]-UDP-3-*O*-(*R*-3-hydroxydecanoyl) GlcNAc. The coding region of the *lpxC* gene was amplified from *P. aeruginosa* genomic DNA using the polymerase chain reaction and cloned into a T7 expression vector, pET21b (Novagen), using *E. coli* DH5α as host strain. Overexpression was achieved by inducing with IPTG. The overexpressed protein was purified by DEAE−Sepharose chromatography followed by phenyl−Sepharose and Q Sepharose chromatography in the presence of EDTA. Activity of the enzyme was restored by the addition of zinc, and the final step of enzyme purification was achieved by passage over a Superdex 75 column.

UDP-3-*O*-(*R*-3-hydroxydecanoyl)-GlcNAc (38 mg, 0.049 mmol) was incubated with a purified preparation of *P. aeruginosa* LpxC enzyme (3.3 mg, specific activity 500 nmol min^{-1} mg^{-1})

at 30 °C and pH 6.7 for 60 min with a further addition of enzyme (1.5 mg) at 30 min. The reaction was stopped with ice-cold ethanol to 80% final concentration, and the mixture was then chilled on ice for 15 min and centrifuged at 15000*g* for 15 min. The supernatant was filtered through 38 g of silica previously equilibrated with ice-cold 80% aqueous EtOH, and the filter cake was washed with an additional 100 mL of the same eluant. The eluted glycolipid solution was concentrated in vacuo to ca. 25 mL, diluted with 75 mL of ice-cold 0.05% pH 5.6 NH_4OAc, and lyophilized. It was determined by analytical HPLC that 58% conversion had occurred, with minimal (<5%) rearrangement of the nascent amine. Purification by preparative reverse-phase HPLC enabled the recovery of both unconverted starting *N*-acetyl compound (eluting between 20 and 25 min) and the primary amine product (eluting between 26 and 34 min). The yield of purified amine [MS, *m*/*z* 736.2 $(M + H)^+$] was 15.1 mg (16%), and 9.2 mg of *N*-acetyl starting material was recovered.

Analytical HPLC: 250 mm × 4.6 mm C18 Luna column, 100 Å, 5 μm column at 1 mL/min, with a linear gradient of 10% to 40% B in A over 40 min, A = 0.05% NH_4OAc in water, pH 5.6, B = acetonitrile, monitoring λ = 260 nm. Preparative HPLC: 250 mm × 10 mm C18 Luna column, 5 μm column at 4.7 mL/min, with a linear gradient of 10% to 40% B in A over 40 min, A = 0.05% NH_4OAc in water, pH 5.6, B = acetonitrile, monitoring λ = 260 nm.

Reacetylation with *N*-([^{3}H]-Acetoxy)phthalimide. Freshly prepared *N*-([^{3}H]-acetoxy)phthalimide (50 μmol, ca. 4 equiv per equivalent of amine substrate, 20 Ci/mmol) was dissolved in 600 μL of dry acetonitrile and was added to a reaction vessel containing UDP-3-*O*-(*R*-3-hydroxydecanoyl)-glucosamine (8.94 mg, 12 μmol) suspended in ca. 1 mL of dry acetonitrile. To this suspension was added dropwise triethylamine (10 equiv per equivalent of amine, 120 μmol, 12.1 mg, 17 μL) dissolved in 183 μL of dry acetonitrile. The reaction mixture was flushed with dry nitrogen and warmed to 35 °C overnight, during which time a strong yellow color developed. Analytical HPLC indicated disappearance of the amine peak at ca. 24 min and concomitant appearance of the N-acetylated peak at ca. 20 min under the conditions described above. The volatiles were removed in vacuo, and the residue was dissolved in HPLC buffer A and purified directly by preparative HPLC, with the product collected between 17 and 19 min: HPLC t_R 18.53 min (81.2 area %) for both ^{3}H and UV_{260} detection, specific activity 14 Ci/mmol. Diagnostic peaks in the ^{3}H NMR spectra (with and without ^{1}H decoupling) and ^{1}H NMR spectra revealed the product and an acyl migration byproduct; these were analyzed by reference to 1D and 2D spectra of the cold material. ^{3}H NMR (D_2O, proton undecoupled) δ 1.90 (t) and 1.85 (t); ^{1}H NMR (300 MHz, D_2O) δ 7.80 (H-6^U, d), 5.81 (H-1′^{U}, d), 5.78 (H-5^U, d), 5.40 (H-1, dd, major), 5.33 (H-1, dd, minor), 5.04 (H-3, t, major), 4.24−4.17 (H-2′^{U} + H-6ab minor), 4.12−4.01 (H-2 + UDP−H-3′,4′,5′ab), 3.83 (H-5 + decanoyl-C^3-H), 3.69 (glc-C^{6}H$_2$), 2.50 (CH_2CO, minor), 2.48 (CH_2CO, major), 1.32 and 1.12 (methylenes), 0.7 (Me). The spectra demonstrate the correct anomeric stereochemistry and the correct regiochemistry for the hydroxydecanoyl group in the major product.

Control experiments with the cold substrate in D_2O buffer (pH* = 6.3) following the slow acyl migration over several weeks revealed that the glc-H-1 at 5.40 ppm correlated with 4.03 (H-2), 5.04 (H-3), 3.59 (H-4), 3.83 (H-5), and ∼3.69 ppm (H-6ab, AB of ABX), while the H-1 at 5.33 ppm correlated with 3.67 (H-2), 3.84 (H-3), 3.44 (H-4, t), 3.96 (H-5, dt), and 4.23 ppm (H-6ab). A minor peak at 4.85 ppm (H-4, t, minor) revealed the intermediate UDP-4-*O*-(*R*-3′-hydroxydecanoyl)-GlcNAc. These acyl migrations have been observed previously.[1a]

***P. aeruginosa* LpxC Inhibition Assay.** The assay followed the general method of Hyland et al.[18] Briefly, samples were incubated with 2 nM *P. aeruginosa* LpxC and 150 nM [^{3}H-Ac]-UDP-3-*O*-(*R*-3-hydroxydecanoyl)-GlcNAc in a total volume of 50 μL for 90 min at room temperature. Reactions were carried out in 96-well polypropylene plates in 50 mM sodium phosphate buffer, pH 7.5, containing 1 mg/mL BSA. Reactions were stopped by the addition of 180 μL of a 3% suspension of activated charcoal powder in 100 mM sodium acetate, pH 7.5. Supernatants were clarified by centrifugation. A portion of the clarified supernatant, containing the enzymatically released [^{3}H]-acetate, was transferred to opaque white 96-well plates containing scintillation fluid. The radioactivity was measured in a Perkin-Elmer/Wallac Trilux Microbeta counter. Control reactions to which 5 mM EDTA had been added were included with each run to determine nonspecific tritium release.

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Supporting Information Available: Chemical synthesis and characterization details for representative benzoic acids and their respective intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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