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Application of the Dakin−West Reaction for the Synthesis of Oxazole-Containing Dual PPARα/γ Agonists

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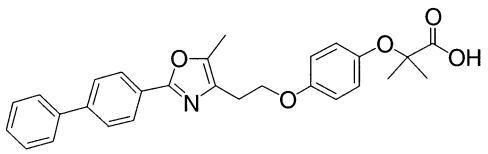
An improved method for the preparation of a series of oxazole-containing dual PPARα/γ agonists is described. A synthetic sequence utilizing a Dakin−West reaction was devised that allows for the introduction of the oxazole ring either late in the synthetic sequence via aminomalonate-derived chemistry or in pivotal SAR intermediates derived from aspartic acid.

We have recently disclosed the structure of **1a**, a dual PPARα/γ agonist, and demonstrated the compound's preclinical beneficial impact on multiple facets of type 2 diabetes and the associated cardiovascular risk.[1] The peroxisome proliferator activated receptor (PPAR) family of nuclear hormone receptors has been identified as key modulators of metabolism since the first member of the receptor family was cloned a decade ago.[2] The profile of a dual PPARα/γ agonist appears well-suited as a treatment for type 2 diabetes[3] because of the insulin-sensitizing/glucose-controlling potential of PPARγ agonists, the molecular target of the thiazolidine-2,4-diones (TZDs),[4] in combination with the positive lipid- and cholesterol-modulating activities of PPARα agonists, the molecular target of the fibrates.[5] Herein we describe the development of a practical synthesis of **1a** and related analogues, utilizing the Dakin−West reaction[6] followed by Robinson−Gabriel cyclodehydration[7] to install substitution at the 5-position of the oxazole ring. The versatility of these historic reactions is further demonstrated using acylated aspartic acid derivatives to prepare a variety of 2-substituted oxazole analogues.



1a

Interest in compound **1a** led to the development of a synthetic route amenable to large-scale execution. Previous preparation of compound **1a,** depicted in Scheme 1, utilized early oxazole ring formation through condensation of butanedione monooxime with 4-bromobenzaldehyde.[8] This route allowed preparation of 2-aryl analogues for structure−activity relationship studies by incorporating straightforward coupling of tosylates of 5-methyl-2-aryl-4-oxazolylethanols (**5**) with 2-(4-hydroxyphenoxy)-2-methylpropanoic acid ethyl ester. However, the sequence offers opportunities for process improvement to avoid several potentially hazardous reagents and intermediates. These include potassium cyanide, diborane, an unstable *N*-oxide intermediate (**2**), and the explosive hazard associated with butanedione monooxime.[9] In addition, attempts to expand the SAR by condensation of the monooxime with certain halogen-substituted aromatic aldehydes (particularly *o*-bromobenzaldehyde) were unsatisfactory.

Results and Discussion

In reviewing the literature for other methods to prepare oxazole-ethanols **6**, the work of Meguro et al. and others[10] suggested aspartic acid β esters **8** could be

(1) (a) Brooks, D. A.; Etgen, G. J.; Rito, C. J.; Shuker, A. J.; Dominianni, S. J.; Warshawsky, A. M.; Ardecky, A.; Paterniti, J. R.; Tyhonas, J.; Karanewsky, D. S.; Kauffman, R. F.; Broderick, C. L.; Oldham, B. A.; Montrose-Rafizadeh, C.; Winneroski, L. L.; Faul, M. M.; McCarthy, J. R. *J. Med. Chem.* **2001**, *44*, 2061. (b) Etgen, G. J.; Oldham, B. A.; Johnson, W. T., Broderick, C. L.; Brozinick, J. T.; Bean J. S.; Bensch, W. R.; Brooks, D. A.; Rito, C. J.; Shuker, A. J.; Kauffman, R. F. *Diabetes* **2002**, *51*, 1083.

(2) (a) Issemann, I.; Green, S. *Nature* **1990**, *347*, 645. (b) Mangelsdorf, D. J.; Evans, R. M. *Cell* **1995**, *83*, 841. (c) Willson, T. M.; Brown, P. J.; Sterbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527.

(3) Auwerx, J. In *Insulin Resistance, Metabolic Disease and Diabetic Complications: Proceedings of the 7th European Symposium on Metabolism*, Padova, Sept 30−Oct 3, 1998; Elsevier: Amsterdam, 1999, p 167.

(4) (a) Sohda, T.; Mizuno, K.; Momose, Y.; Ikeda, H.; Fujita, T.; Meguro, K. *J. Med. Chem.* **1992**, *35*, 2617. (b) Hulin, B.; Clark, D. A.; Goldstein, S. W.; McDermott, R. E.; Dambek, P. J.; Kappeler, W. H.; Lamphere, C. H.; Lewis, D. M.; Rizzi, J. P. *J. Med. Chem.* **1992**, *35*, 1853. (c) Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M.; Kliewer, S. A. *J. Biol. Chem.* **1995**, *270*, 12953. (d) Nomura, M.; Kinoshita, S.; Satoh, H.; Maeda, T.; Murakami, K.; Tsunoda, M.; Miyachi, H.; Awano, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 533.

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(6) (a) Dakin, H. D.; West, R. *J. Biol. Chem.* **1928**, *91*, 745. (b) Buchanan, G. L. *Chem. Soc. Rev.* **1988**, *17*, 91.

(7) (a) Robinson, R. *J. Chem. Soc.* **1909**, *95*, 2167. (b) Gabriel, S. *Chem. Ber.* **1910**, *43*, 134, 1283.

(8) Goto, Y.; Yamazaki, M.; Hamana, M. *Chem. Pharm. Bull.* **1971**, *19*, 2050.

(9) Diacetyl monooxime, CAS [57-71-6], OHS Material Safety Data Sheet.

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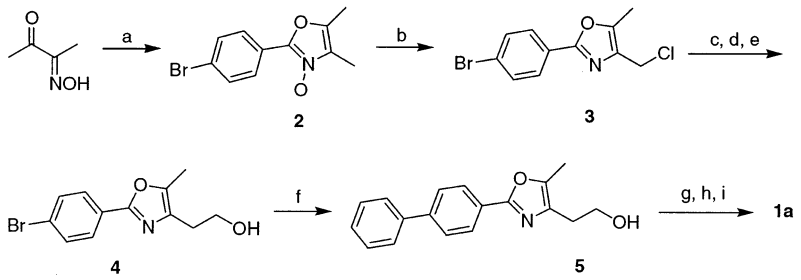
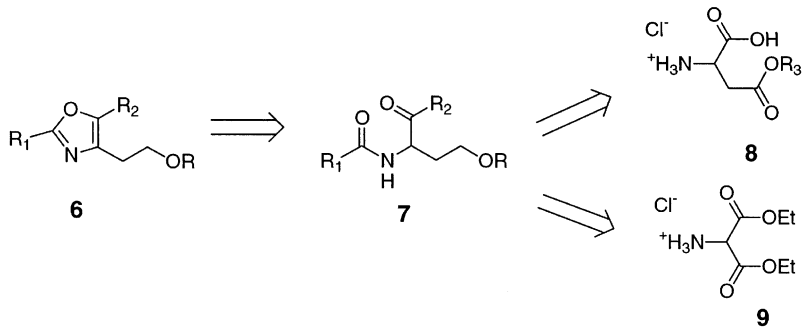
SCHEME 1. Preparation of 1a from Butanedione Monooxime[a]

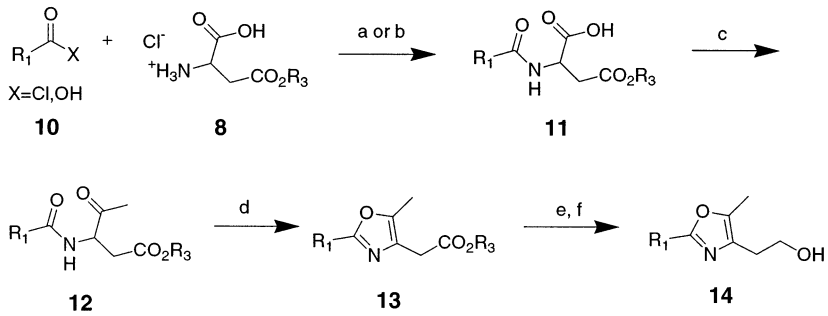


[a] (a) *p*-Bromobenzaldehyde, HOAc, HCl (74%); (b) $POCl_3$, $CHCl_3$ (72%); (c) KCN, KI, DMF (100%); (d) KOH, 2-methoxyethanol (60%); (e) BH_3−THF; MeOH (72%); (f) $PhB(OH)_2$, $Pd(OAc)_2$, PPh_3 (95%); (g) $(Ts)_2O$, Pyr, DMAP (95%); (h) 2-(4-hydroxyphenoxy)-2-methylpropanoic acid ethyl ester, Cs_2CO_3, DMF (50%); NaOH, EtOH (68%).

SCHEME 2. Retrosynthetic Analysis



SCHEME 3. Analogues 14 from Aspartic Acid *β* Esters 8[a]



[a] (a) Na_2CO_3, acetone, H_2O, 0 °C; (b) NMM, 2-Cl-4,6-dimethoxy-1,3−5-triazine; (c) acetic anhydride, pyridine, 90 °C; (d) $POCl_3$, DMF, 90 °C or H_2SO_4, Ac_2O, 90 °C; (e) KOH or NaOH, EtOH; (f) BH_3−THF; MeOH, 50 °C.

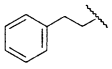
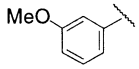
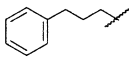
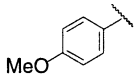
utilized as the starting material to provide **1a** and related analogues. The sequence would involve acylation to differentiate R_1, Dakin−West conversion to the keto-amide to introduce R_2, cyclodehydration to the oxazole ring, and reduction of the ester side chain. Alternatively, it was envisioned that the synthesis of **1a** and related analogues from inexpensive aminodiethyl malonate hydrochloride **9** was possible via simple acylation to attach the biphenyl unit, followed by the Sorensen method[11] for amino acid incorporation into the side chain. The resulting amino acid could be converted to the keto-amide via a Dakin−West reaction prior to cyclodehydration to provide the central oxazole ring. Aspartic acid *β* esters **8** provided direct access to key oxazol-4-yl ethanol SAR intermediates with incorporation of a variety of aryl or alkyl substitution at the 2-position of the oxazole ring. In the preparation of intermediates related to alcohol **5**, aspartic acid methyl (or benzyl) ester hydrochloride salt was acylated with the appropriate acid or acid chloride. Dakin−West conditions (acetic anhydride, pyridine) were then utilized to install the 5-methyl group (**12**) prior to Robinson−Gabriel cyclodehydration to provide oxazole esters **13** in three steps (Scheme 3).[12] Cyclodehydration

(10) (a) Meguro, K.; Tawada, H.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1986**, *34*, 2840. (b) Hulin, B.; Clark, D. A.; Goldstein, S. W.; McDermott, R. E.; Dambek, P. J.; Kappeler, W. H.; Lamphere, C. H.; Lewis, D. M.; Rizzi, J. P. *J. Med. Chem.* **1992**, *35*, 1853. (c) Collins, J. L.; Blanchard, S. G.; Boswell. G. E.; Charifson, P. S.; Cobb, J. E.; Henke, B. R.; Hull-Ryde, E. A.; Kazmierski, W. M.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J.; Lenhard, J. M.; Orband-Miller, L. A.; Gray-Nunez, Y.; Parks, D. J.; Plunkett, K. D.; Tong, W.-Q. *J. Med. Chem.* **1998**, *41*, 5037.

(11) (a) Sorensen, S. P. L. *C. R. Trav. Lab. Carlsberg, Ser. Chim.* **1903**, *6*,1. (b) Sorensen, S. P. L.; Andersen, A. C. *Z. Physiol. Chem.* **1905**, *44*, 448. (c) Sorensen, S. P. L. *Z. Physiol. Chem.* **1908**, *56*, 236.

(12) The workup could be simplified by conducting the acylation step in the presence of PVP (4% cross-linked polyvinyl pyridine), which could be readily removed from the reaction mixture via filtration. Treatment of the ether-diluted filtrate with concentrated sulfuric acid (1 equiv) at room temperature for 2 h then provided direct formation of the oxazole product in yields comparable to the two-step procedure (40−50% following chromatography).

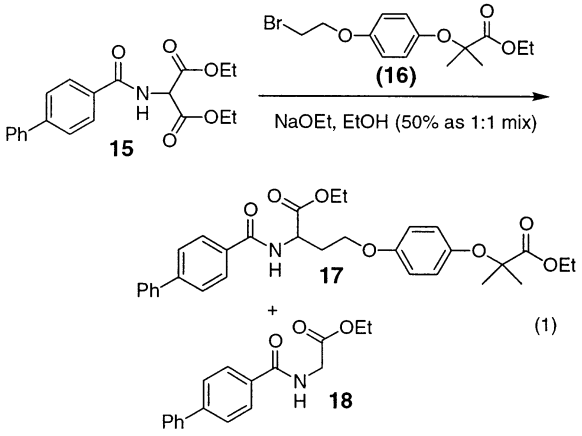
TABLE 1. Oxazol-4-yl Acetic Acid Ester Products 12 and 13

	R_3 = Bn				R_3 = Me		
	R_1	Dakin-West (12) % Yield	Robinson-Gabriel (13) % Yield		R_1	Dakin-West (12) % Yield	Robinson-Gabriel (13) % Yield
a		68	86[a]	**e**		52	72[b]
b		58	80[b]	**f**		69	46[b]
c		91	98[a]	**g**		68	81[b]
d		94	84[a]				

[a] Method A: $POCl_3$, DMF, 90 °C. [b] Method B: H_2SO_4, Ac_2O, 90 °C.

was carried out at 90 °C for 30 min with either phosphorus oxychloride in DMF (Method A) or catalytic sulfuric acid in acetic anhydride (Method B). In our hands, superior yields were found in this series using $POCl_3$ for aromatic substrates (**13c,d**), whereas aliphatic substrates generally gave better results with Method B. Hydrolysis of the ester and reduction of the acid with borane−THF afforded alcohols **14**. Table 1 summarizes the formation of oxazol-4-yl acetic acid esters **13a**−**g** in good to excellent yields.

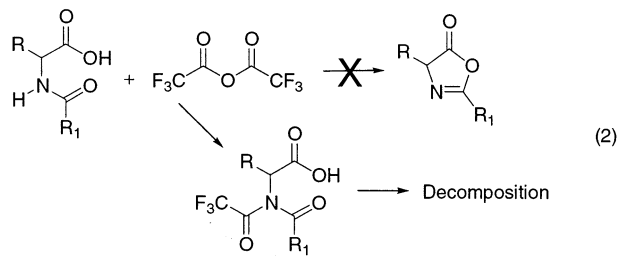
Evaluation of the utility of aminodiethyl malonate hydrochloride (**9**) as a starting material began with the coupling of **9** with 4-biphenylcarbonyl chloride in *N*-methylpyrrolidinone and triethylamine as the base to provide amide **15** in 98% yield. Alkylation of **15** with **16** provided low yields (~50%) of **17**. The expected tri-ester product was never observed or isolated. When NaOEt was used as the base in ethanol or DMF, a competing decarboxylation of **15** provided the glycine derivative **18**. Other bases such as NaH gave similar results. The competing decarboxylation reaction may be due to dianion formation of the acidic nitrogen proton and could potentially be avoided by the use of an acetyl-protecting group to decrease the acidity of this proton.



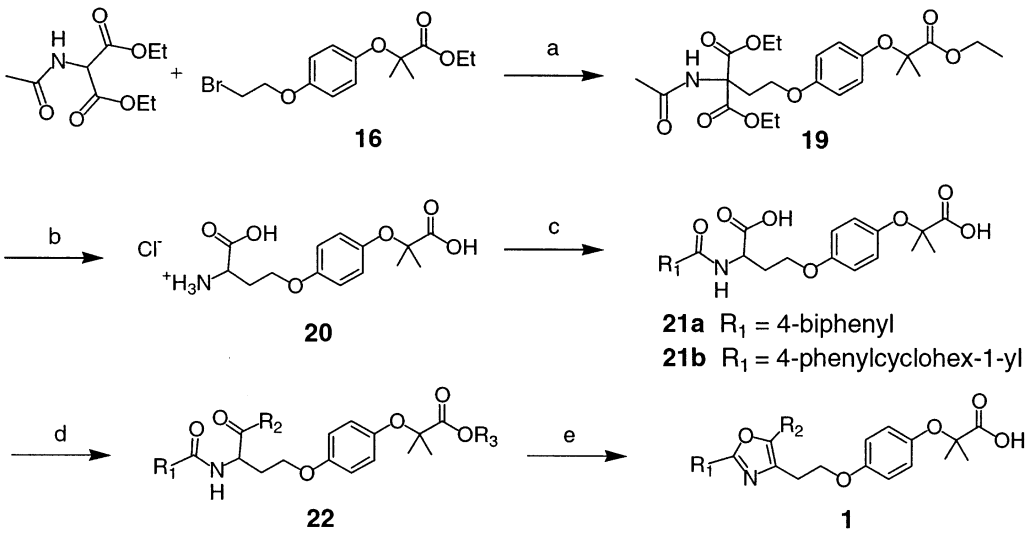
Indeed, alkylation of inexpensive *N*-acetylaminodimethyl malonate with **16**, as shown in Scheme 4, yielded **19** in 89% with sodium hydride in DMF. Triester **19** was converted to crystalline **20** with concentrated HCl and acylated with 4-biphenylcarbonyl chloride using triethylamine in *N*-methylpyrrolidinone to provide **21a**. The material was submitted directly to the Dakin−West conditions of pyridine and acetic anhydride at 90 °C to effect conversion of the carboxylic acid to methyl ketone **22a** in excellent yield. Cyclodehydration of **22a** was optimized with acetic anhydride and sulfuric acid in refluxing ethyl acetate to generate the desired product **1a** in 87% yield after crystallization from EtOAc/heptane. This convergent five-step route was found to be scalable with excellent, reproducible overall yield and was preferable to the aspartic acid route on the basis of cost of starting materials.

Compound **20** could be acylated with other acid chlorides including 4-phenylcyclohexylcarbonyl chloride to provide **21b**. Additional 5-position analogues were prepared from the common late-stage intermediate **21a** using *n*-butyric anhydride and benzoic anhydride (**1b,c**). In the preparation of analogues **1b**−**d**, small-scale purification to remove residual acid was best achieved by conversion to the methyl ester of **22b**−**d** with diazomethane prior to cyclodehydration with phosphorus oxychloride in DMF. Hydrolysis to **1b**−**d** was straightforward with NaOH in EtOH.

Preparation of the 5-trifluoromethyl derivative **1e** (eq 2) necessitated modification of the original procedure since reaction of **21a** with TFAA in pyridine led to complete decomposition of the starting material. Reacting the primary *N*-acyl amino acid directly with TFAA is likely problematic because *N*-acylation is competitive with oxazolone formation.



SCHEME 4. Synthesis of 1 and Analogues from *N*-Acylaminodiethylmalonate[a]

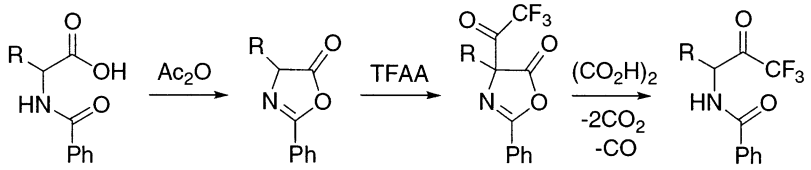


	R_1	R_2	Yield (%)
22a	4-Ph-Ph	Me	95[b]
22b	4-Ph-Ph	n-Pr	73[c]
22c	4-Ph-Ph	Ph	73[c]
22d	4-Ph-C_6H_{14}	Me	99[c]

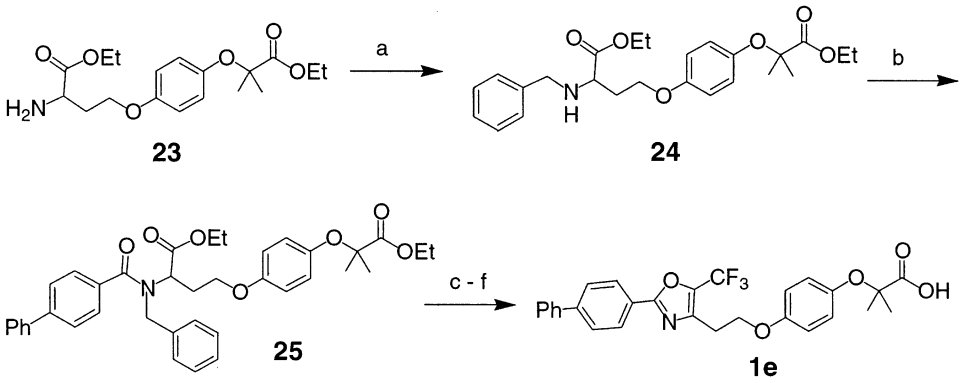
	R_1	R_2	Yield (%)	Method
1a	4-Ph-Ph	Me	87	A
1b	4-Ph-Ph	n-Pr	80	B
1c	4-Ph-Ph	Ph	80	B
1d	4-Ph-C_6H_{14}	Me	92	B

[a] (a) NaH, DMF (89%); (b) conc HCl (78%); (c) 4-biphenylcarbonyl chloride, Et_3N, NMP or 4-phenylcyclohexylcarbonyl chloride, Et_3N, CH_2Cl_2; (d) $(RCO)_2O$, pyridine; (e) H_2SO_4, Ac_2O, EtOAc (Method A) or $POCl_3$, DMF (Method B). [b] R_3 = H. [c] R_3 = Me, isolated yield following conversion to the methyl ester with diazomethane.

SCHEME 5



SCHEME 6. Preparation of the 5-CF_3-Oxazole Analogue 1e[a]



[a] (a) $NaHB(OAc)_3$, benzaldehyde (64%); (b) 4-biphenylacetyl chloride, Et_3N, CH_2Cl_2 (100%); (c) NaOH, dioxane; (d) $(CF_3CO)_2O$, pyridine; (e) CH_2N_2, CH_2Cl_2 (25%, 3 steps); (f) NaOH, EtOH (98%).

This observation is consistent with those of Kolb and co-workers,[13] who have shown that producing the oxazolone a priori and subsequent reaction with TFAA yields the requisite trifluoromethyl ketone on acid-catalyzed decarboxylation of the acylated intermediate (Scheme 5).

The Kawase[14] protocol using *N*-acyl-*N*-benzyl-α-amino acids was successfully adopted starting with **23**, the diethyl ester derivative of **20**, as shown in Scheme 6. Treatment of **23** with benzaldehyde under reductive

(13) Kolb, M.; Barth, J.; Neises, B. *Tetrahedron Lett.* **1986**, *27*, 1579.

(14) (a) Kawase, M. *Heterocycles* **1993**, *36*, 2441. (b) Kawase, M.; Miyamae, H.; Kurihara, T. *Chem. Pharm. Bull.* **1998**, *46*, 749. (c) Kawasi, M.; Miyamae, H.; Narita, M.; Kurihara, T. *Tetrahedron Lett.* **1993**, *34*, 859. (d) Kawase, M. *Tetrahedron Lett.* **1994**, *35*, 149.

amination conditions provided **24** in 64% yield followed by *N*-acylation with biphenyl-4-carbonyl chloride to give **25** in quantitative yield. Following hydrolysis to the diacid, formation of the oxazole is afforded directly on treatment with trifluoroacetic anhydride in the presence of pyridine to give **1e**. In practice the crude acid product obtained was further esterfied to facilitate purification by normal phase chromatography in 25% yield and then saponified to back to **1e** in 98% yield.

In conclusion, the application of the Dakin−West reaction, coupled with the Robinson−Gabriel reaction, was applied to develop a practical means to **1a**. This methodology offered several opportunities for process improvement over the reported procedure and enabled the multi-kilogram synthesis of **1a**. In addition, the method was useful for the rapid preparation of a wide variety of 2,4,5-substituted oxazole-containing SAR intermediates and products from readily available starting materials.

Experimental Section

General Methods. Commercially available reagents and solvents were used without further purification unless otherwise noted. Melting points are uncorrected. For NMR, chemical shifts are reported in ppm relative to residual nondeuterated solvent. For analytical HPLC measurements, various isocratic methods were used as appropriate to achieve optimal resolution using the indicated percentage of acetonitrile/0.03M phosphate buffer, such as 40% ISO, 60% ISO, and 80% ISO; flow rate 1.5 mL/min; column Zorbax SB-C18, 4.6 mm × 250 mm, 5 μm; 220 nm detection. A gradient method was applied for compound **16** using a 15 min gradient of 40% acetonitrile/60% 0.1% aqueous trifluouroacetic acid to 80% acetonitrile/20% 0.1% aqueous trifluouroacetic acid; flow rate 1.0 mL/min; column Zorbax SB-phenyl, 4.6 mm × 250 mm, 5 μm; 225 nm detection. Elemental analysis was performed by a microanalytical lab, and high-resolution mass spectrometry data was provided by the Physical Chemistry group of Lilly Research Laboratories. Organic solutions were dried over magnesium sulfate unless otherwise specified. Flash column chromatography was carried out using silica gel (230−400 mesh) with EtOAc/hexanes as an eluent. Preparative reversed-phase separations (C-18 silica columns) were carried out using water/acetonitrile gradient programs. Diazomethane solution was prepared as follows: 1-Methyl-3-nitro-1-nitrosoguanidine (1.2 equiv) was slowly added to a stirring mixture of 5.0 N KOH (1.2 equiv) and ethyl ether (0.14 M) at room temperature. The biphasic mixture was stirred for an additional 10 min followed by separation and direct use of the organic phase. Starting amides **11a**−**h** were prepared by literature methods[15] as described in Supporting Information.

3-(Cyclohexanecarbonyl-amino)-4-oxo-pentanoic Acid Benzyl Ester (12a). A mixture of 2-(cyclohexanecarbonyl-amino)-succinic acid 4-benzyl ester 1.72 g, 5.16 mmol), pyridine (5 mL), and acetic anhydride (3 mL) was heated at 90 °C for 2 h. Excess acid anhydride and pyridine were removed under reduced pressure, and the residue was then diluted with ether (150 mL). The organic phase was then washed successively with 1.0 N HCl (50 mL) and water (50 mL), then dried over solid sodium chloride, decanted, and concentrated under reduced pressure to yield an oil. The residue was purified by column chromatography (EtOAc/hexanes) to provide 1.16 g (68% yield) of the desired product as a pale yellow oil. HPLC (>99.9 area%, t_R = 5.8 min at 60% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 6.62 (d, J = 7.5 Hz, 1 H), 5.12 (s, 2 H), 4.76 (ddd, J = 8.5, 4.4, 4.3 Hz, 1 H), 3.04 (B of ABX, J_{BA} = 17.0 Hz, J_{BX} = 4.8 Hz, 1H), 2.83 (A of ABX, J_{AB} = 17.0 Hz, J_{AX} = 4.4 Hz, 1H), 2.22 (s, 3 H), 2.12 (tt, J = 11.6, 3.4 Hz, 1 H), 1.77 (m, 5 H), 1.33 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.06, 27.09, 29.83, 29.90, 35.65, 45.60, 55.11, 55.16, 67.26, 128.53, 128.83, 135.42, 171.49, 175.91, 205.59; MS *m*/*z* 332.2 $(M + H)^+$.

3-[(Cyclohex-1-enecarbonyl)-amino]-4-oxo-pentanoic Acid Benzyl Ester (12b). The title compound was prepared by the method described for **12a** and obtained as an oil in 58% yield after normal phase chromatography. HPLC (96.9 area%, t_R = 4.4 min at 60% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5 H), 6.89 (d, J = 7.9 Hz, 1 H), 6.64 (m, 1 H), 5.12 (s, 2 H), 4.83 (ddd, J = 8.5, 4.4, 4.3 Hz, 1 H), 3.07 (B of ABX, J_{BA} = 17.1 Hz, J_{BX} = 4.8 Hz, 1H), 2.86 (A of ABX, J_{AB} = 17.1 Hz, J_{AX} = 4.4 Hz, 1H), 2.24 (s, 3 H), 2.19 (m, 3 H), 1.65 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.67, 171.55, 168.13, 135.40, 135.30, 132.53, 128.84, 128.67, 128.54, 67.27, 55.40, 55.32, 35.65, 27.17, 25.90, 24.47, 22.48, 21.86; MS *m*/*z* 330.2 $(M + H)^+$.

3-(3-Methoxy-benzoylamino)-4-oxo-pentanoic Acid Benzyl Ester (12c). The title compound was prepared by the method described for **12a** and obtained as a solid in 91% yield after normal phase chromatography. Mp 56−57 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.96 (d, J = 7.7 Hz, 1H), 7.41 (m, 3H), 7.31 (m, 5H), 7.13 (m, 1H), 5.11 (s, 2H), 4.79 (m, 1H), 3.81 (s, 3H), 2.88 (A of ABX, J_{AB} = 16.1 Hz, J_{AX} = 4.2 Hz, 1H), 2.86 (B of ABX, J_{BA} = 16.1 Hz, J_{BX} = 2.7 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.43, 166.07, 159.17, 135.96, 134.92, 129.49, 128.28, 127.88, 127.71, 119.54, 117.37, 112.60, 101.93, 90.08, 65.63, 55.72, 55.26, 34.31, 26.34; MS *m*/*z* 365.20 $(M + H)^+$.

3-(4-Methoxy-benzoylamino)-4-oxo-pentanoic Acid Benzyl Ester (12d). The title compound was prepared by the method described for **12a** and obtained as a solid in 94% yield after normal phase chromatography. Mp 115 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.82 (d, J = 7.7 Hz, 1H), 7.84 (d, J = 8.7 Hz, 2H), 7.32 (m, 5H), 7.02 (d, J = 8.7 Hz, 2H), 5.11 (s, 2H), 4.77 (m, 1H), 3.82 (s, 3H), 2.87 (A of ABX, J_{AB} = 16.1 Hz, J_{AX} = 4.2 Hz, 1H), 2.85 (B of ABX, J_{BA} = 16.1 Hz, J_{BX} = 2.7 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.49, 165.80, 161.85, 135.97, 129.23, 128.29, 127.87, 127.70, 125.71, 113.54, 92.05, 90.07, 65.60, 55.67, 55.34, 34.40, 26.30; MS *m*/*z* 365.20 $(M + H)^+$.

4-Oxo-3-phenylacetylamino-pentanoic Acid Methyl Ester (12e). The title compound was prepared by the method described for **12a** and obtained as an oil in 52% yield after normal phase chromatography. HPLC (>99.9 area%, t_R = 2.1 min at 60% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 6.61 (d, J = 7.5 Hz, 1 H), 4.71 (ddd, J = 8.6, 4.6, 4.4 Hz, 1 H), 3.62 (s, 2 H), 3.61 (s, 3H), 2.95 (B of ABX, J_{BA} = 16.7 Hz, J_{BX} = 4.8 Hz, 1H), 2.74 (A of ABX, J_{AB} = 16.7 Hz, J_{AX} = 4.4 Hz, 1H), 2.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.94, 171.45, 170.57, 134.12, 129.04, 128.88, 127.33, 55.04, 52.08, 43.69, 34.97, 26.70; MS *m*/*z* 264.1 $(M + H)^+$.

4-Oxo-3-(3-phenyl-propionylamino)-pentanoic Acid Methyl Ester (12f). The title compound was prepared by the method described for **12a** and obtained as an oil in 69% yield after normal phase chromatography. HPLC (>99.9 area%, t_R = 2.3 min at 60% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 5 H), 6.60 (d, J = 7.9 Hz, 1 H), 4.71 (ddd, J = 8.5, 4.4, 4.3 Hz, 1 H), 3.64 (m, 3 H), 2.99 (t, J = 7.0 Hz, 2 H), 2.93 (B of ABX, J_{BA} = 17.2 Hz, J_{BX} = 4.8 Hz, 1H), 2.66 (A of ABX, J_{AB} = 17.2 Hz, J_{AX} = 4.4 Hz, 1H), 2.57 (t, J = 7.0 Hz, 2 H), 2.11 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.59, 172.10, 172.00, 140.49, 128.74, 128.55, 126.52, 55.12, 52.43, 38.57, 35.32, 31.92, 27.00; MS *m*/*z* 278.1 $(M + H)^+$.

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4-Oxo-3-(4-phenyl-butyrylamino)-pentanoic Acid Methyl Ester (12g). The title compound was prepared by the method described for **12a** and obtained as an oil in 68% yield after normal phase chromatography. HPLC (93.3 area%, t_R = 2.8 min at 60% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2 H), 7.19 (m, 3 H), 6.62 (d, J = 7.91 Hz, 1 H), 4.76 (ddd, J = 8.02, 4.61, 4.50 Hz, 1 H), 3.68 (s, 3 H), 2.99 (B of ABX, J_{BA} = 16.9 Hz, J_{BX} = 4.8 Hz, 1H), 2.80 (A of ABX, J_{AB} = 16.9 Hz, J_{AX} = 4.4 Hz, 1H), 2.67 (m, 2 H), 2.26 (m, 2 H), 2.24 (s, 3 H), 2.00 (dt, J = 14.94, 7.47 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.36, 172.66, 172.05, 141.40, 128.67, 128.63, 128.60, 55.33, 52.54, 36.09, 35.49, 27.43, 27.13; MS m/z 292.1 $(M + H)^+$.

(2-Cyclohexyl-5-methyl-oxazol-4-yl)-acetic Acid Benzyl Ester (13a). Method A. Phosphorus oxychloride (22 mL, 0.235 mol, 3.0 equiv) was added dropwise to a solution of 3-(cyclohexanecarbonyl-amino)-4-oxo-pentanoic acid benzyl ester 26.0 g, 0.078 mol) in DMF (330 mL). The mixture was heated to 90 °C for 30 min and then cooled to ambient temperature before being diluted by the slow addition of DI water (600 mL; **Caution exothermic**). The mixture was cooled to ambient temperature and extracted with MTBE. The combined organic phases were washed with DI water and brine (150 mL), dried, and concentrated to obtain 21.1 g (86%) as a brown oil. Further purification was not necessary. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.27 (m, 5H), 5.11 (s, 2H), 3.49 (s, 2H), 2.68 (tt, J = 11.6, 3.6 Hz, 1H), 2.17 (s, 3H), 2.01−1.97 (m, 2H), 1.76 (dt, J = 12.8, 3.6 Hz, 2H), 1.68−1.63 (m, 1H), 1.41 (qd, J = 12.0, 3.2 Hz, 1H), 1.33−1.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.88, 144.09, 136.06, 128.24, 127.82, 127.55, 127.41, 65.56, 36.31, 31.38, 30.09, 28.57, 25.27, 24.85, 9.48; MS m/z 314.1 $(M + H)^+$.

(2-Cyclohex-1-enyl-5-methyl-oxazol-4-yl)-acetic Acid Benzyl Ester (13b). The title compound was prepared by the method described for **13f** and obtained as a clear oil in 80% yield after normal phase chromatography. HPLC (>99.9 area%, t_R = 4.0 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 6.67 (ddd, J = 4.06, 2.20, 2.09 Hz, 1 H), 5.15 (s, 2 H), 3.55 (s, 2 H), 2.45 (m, 2 H), 2.25 (s, 3 H), 2.22 (m, 2 H), 1.70 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.89, 160.54, 144.22, 135.54, 129.98, 128.24, 128.11, 127.92, 125.81, 66.58, 32.13, 25.42, 24.61, 22.12, 21.85, 10.24.

[2-(3-Methoxy-phenyl)-5-methyl-oxazol-4-yl]-acetic Acid Benzyl Ester (13c). The title compound was prepared by the method described for **13a** and obtained as solid in 98% yield after normal phase chromatography. Mp 63−64 °C; FTIR (CHCl3) 3019, 1737, 1555, 1492, 1467, 1204, 1159, 672; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51−7.34 (m, 8H), 7.06 (m, 1H), 5.15 (s, 2H), 3.82 (s, 3H), 3.71 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.82, 159.55, 158.18, 146.03, 136.02, 130.26, 129.14, 128.33, 128.16, 127.94, 127.76, 117.78, 116.31, 110.10, 65.81, 55.21, 31.38, 9.76; MS m/z 360.1 $(M + H)^+$.

[2-(4-Methoxy-phenyl)-5-methyl-oxazol-4-yl]-acetic Acid Benzyl Ester (13d). The title compound was prepared by the method described for **13a** and obtained as solid in 84% yield after normal phase chromatography. HPLC (99.3 area%, t_R = 3.1 min at 80% ISO); mp 95.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.8 Hz, 2H), 7.36−7.31 (m, 5H), 6.94 (d, J = 8.8 Hz, 2H), 5.18 (s, 2H), 3.85 (s, 3H), 3.60 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 161.2, 159.8, 145.3, 136.0, 129.2, 128.7, 128.4, 127.9, 120.7, 114.3, 114.2, 67.0, 55.6, 32.4, 10.5; HRMS-ES m/z $[M + H]^+$ calcd for $C_{20}H_{20}NO_4$ 338.1385, found 338.1392. Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.25; H, 5.70; N, 4.18.

(2-Benzyl-5-methyl-oxazol-4-yl)-acetic Acid Methyl Ester (13e). The title compound was prepared by the method described for **13f** and obtained as solid in 72% yield after reverse phase chromatography. HPLC (98.0 area%, t_R = 3.2 min at 60% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5 H), 4.04 (s, 2 H), 3.72 (s, 3 H), 3.47 (s, 2 H), 2.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.37, 160.29, 145.21, 135.40, 128.44, 128.30, 127.49, 126.60, 51.96, 34.59, 31.71, 10.04; MS m/z 246.08 $(M + H)^+$.

(5-Methyl-2-phenethyl-oxazol-4-yl)-acetic Acid Methyl Ester (13f). Method B. To 4-oxo-3-(3-phenyl-propionylamino)-pentanoic acid methyl ester (10 g, 36 mmol) and acetic anhydride (28 mL) was added concentrated H_2SO_4 (1 mL). The solution was heated to 90 °C for 30 min and then cooled to ambient temperature. The reaction was slowly diluted with DI water (30 mL, potential exotherm). The reaction mixture was partitioned between CH_2Cl_2 and water. The organic phase was washed with DI water, 10% aqueous $NaHCO_3$, brine, dried, and concentrated to obtain a brown oil. The residue was purified by column chromatography (35% EtOAc/hexanes) to provide the desired product (3.25 g) as a pale, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.20 (m, 5H), 3.72 (s, 3H), 3.47 (s, 2H), 3.08−2.96 (m, 4H), 2.24 (s, 3H); MS m/z 260 $(M + H)^+$.

[5-Methyl-2-(3-phenyl-propyl)-oxazol-4-yl]-acetic Acid Methyl Ester (13g). The title compound was prepared by the method described for **13f** and obtained as solid in 81% yield after reverse phase chromatography. HPLC (99.0 area%, t_R = 4.8 min at 60% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2 H), 7.17 (m, 3 H), 3.71 (s, 3 H), 3.46 (s, 2 H), 2.70 (m, 4 H), 2.24 (s, 3 H), 2.07 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.45, 161.99, 144.46, 141.04, 128.17, 128.03, 127.19, 125.61, 51.96, 35.11, 31.71, 28.57, 27.51, 10.01; MS m/z 274.11 $(M + H)^+$.

2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethanol (14a). (2-Cyclohexyl-5-methyl-oxazol-4-yl)-acetic acid benzyl ester (54.8 g, 0.174 mol), 2B-3 ethanol (276 mL), DI water (230 mL), and KOH (23.0 g, 0.349 mol) were stirred at ambient temperature for 60 min. The reaction mixture was concentrated, diluted with water (150 mL), and extracted three times with MTBE. The MTBE layers were discarded. The aqueous layer was acidified and extracted three times with MTBE. The combined MTBE layers were washed with brine, dried, and concentrated to obtain 34.17 g of (2-cyclohexyl-5-methyl-oxazol-4-yl)-acetic acid.

BH_3−THF complex (96 mL, 0.096 mol, 2.3 equiv) was added dropwise to a solution of (2-cyclohexyl-5-methyl-oxazol-4-yl)-acetic acid (34.17 g, 0.153 mol) in THF (164 mL). The reaction mixture was stirred for 3 h and then quenched with MeOH (130 mL). After stirring overnight at room temperature, the mixture was heated at 60 °C for 2 h, cooled to ambient temperature, and concentrated. The residue was dissolved in CH_2Cl_2 (185 mL), washed with 1 N NaOH and brine, dried, and concentrated under reduced pressure to obtain **14a** (33.23 g, 91% from **13a**) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (t, J = 6.8 Hz, 2H), 2.58 (tt, J = 11.6, 3.6 Hz, 1H), 2.54 (t, J = 6.8 Hz, 2H), 2.13 (s, 3H), 1.93−1.89 (m, 2H), 1.74 (dt, J = 12.8, 3.6 Hz, 2H), 1.67−1.62 (m, 1H), 1.41 (qd, J = 12.0, 3.2 Hz, 1H), 1.33−1.17 (m, 4H); ^{13}C NMR (75 MHz, d_6-DMOS) δ 164.37, 142.55, 131.13, 59.96, 36.42, 30.16, 29.16, 25.29, 24.93, 9.52; MS m/z 210.1 $(M + H)^+$, 232.1 $(M + H + Na)^+$. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.88; H, 9.15; N, 6.69. Found: C, 68.56; H, 9.04; N, 6.43.

2-(2-Cyclohex-1-enyl-5-methyl-oxazol-4-yl)-ethanol (14b). Hydrolysis of ester **13b** by the procedure described for **14a** provided (2-cyclohex-1-enyl-5-methyl-oxazol-4-yl)-acetic acid (t_R = 2.6 min at 60% ISO), which was reduced by the procedure described for **14a** to provide **14b** as a clear oil following normal phase chromatography (76% for two steps). HPLC (99.1 area%, t_R = 3.3 min at 60% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (m, 1 H), 3.82 (t, J = 5.93 Hz, 2 H), 3.57 (s, 1 H), 2.62 (t, J = 5.71 Hz, 2 H), 2.39 (m, 2 H), 2.22 (s, 3 H), 2.19 (m, 2 H), 1.67 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.55, 142.58, 132.67, 130.10, 125.77, 61.82, 28.16, 25.47, 24.58, 22.15, 21.88, 10.07; MS m/z 208.04 $(M + H)^+$.

2-[2-(3-Methoxy-phenyl)-5-methyl-oxazol-4-yl]-ethanol (14c). Hydrolysis of ester **13c** by the procedure described for **14a** provided [2-(3-methoxy-phenyl)-5-methyl-oxazol-4-yl]-acetic acid. HPLC (99.1 area%, t_R = 2.3 min at 60% ISO); mp 166.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (dt, J = 8.0, 1.6 Hz, 1H), 7.41−7.36 (m, 2H), 7.03 (ddd, J = 7.6, 2.8, 1.2 Hz, 1H), 3.79 (s, 2H), 3.49 (s, 2H), 2.32 (s, 3H)); ^{13}C NMR (100

MHz, $CDCl_3$) δ 172.2, 160.3, 158.7, 146.5, 131.1, 130.8, 129.0, 118.4, 117.0, 110.7, 55.6, 32.3, 10.3. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.89; H, 5.34; N, 5.65).

[2-(3-Methoxy-phenyl)-5-methyl-oxazol-4-yl]-acetic acid was reduced by the procedure described for **14a** to provide **14c** as a white solid. HPLC (99.4 area%, t_R = 2.5 min at 60% ISO); mp 70.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 6.4, 1.2 Hz, 1H), 7.48 (dd, J = 2.4, 1.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 6.95 (ddd, J = 5.6, 2.6, 1.2 Hz, 1H), 3.92 (t, J = 5.6 Hz, 2H), 3.86 (s, 3H), 3.37 (br s, 1H), 2.71 (t, J = 5.6 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 159.6, 144.4, 134.1, 130.0, 128.9, 118.7, 116.6, 110.8, 62.0, 55.6, 28.4, 10.3; HRMS−FAB m/z $[M + H]^+$ calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1127. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.50; H, 6.53; N, 5.94.

2-[2-(4-Methoxy-phenyl)-5-methyl-oxazol-4-yl]-ethanol (14d). Hydrolysis of ester **13d** by the procedure described for **14a** provided [2-(4-methoxy-phenyl)-5-methyl-oxazol-4-yl]-acetic acid (97.7 area%, t_R = 2.3 min at 60% ISO), which was reduced by the procedure described for **14a** to provide **14d** as a white solid (78% for two steps). Mp 78 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.81 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.59 (t, J = 5.7 Hz, 1H), 3.79 (s, 3H), 3.61 (q, J = 7.0 Hz, 2H), 2.57 (t, J = 7.0 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.20, 157.89, 143.47, 132.94, 126.81, 119.83, 114.20, 59.93, 55.23, 29.33, 9.89; MS m/z 234.02 $(M + H)^+$. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.96; H, 6.49; N, 5.94.

2-(2-Benzyl-5-methyl-oxazol-4-yl)-ethanol (14e). Hydrolysis of ester **13e** by the procedure described for **14a** provided (2-benzyl-5-methyl-oxazol-4-yl)-acetic acid (>99.9 area%, t_R = 4.0 min at 40% ISO), which was reduced by the procedure described for **14a** to provide **14e** as a clear oil following normal phase chromatography (74% for two steps). HPLC (>99.9 area%, t_R = 4.1 min at 40% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5 H), 4.02 (s, 2 H), 3.86 (t, J = 5.71 Hz, 2 H), 3.00 (s, 1 H), 2.64 (t, J = 5.71 Hz, 2 H), 2.21 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.37, 143.86, 135.45, 131.86, 128.51, 128.40, 126.71, 61.51, 34.64, 28.30, 9.98; MS m/z 218.04 $(M + H)^+$.

2-(5-Methyl-2-phenethyl-oxazol-4-yl)-ethanol (14f). (5-Methyl-2-phenethyl-oxazol-4-yl)-acetic acid methyl ester (8.75 g, 33.8 mmol), in MeOH (120 mL) was treated with 5 N NaOH (40 mL), and then the solution was warmed to 40 °C. After 40 min, the reaction mixture was concentrated under reduced pressure, suspended in water, and then acidified to pH = 1 with 5 N HCl. The mixture was extracted with EtOAc, dried, and concentrated to provide 5.25 g (63%) of (5-methyl-2-phenethyl-oxazol-4-yl)-acetic acid as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.20 (m, 5H), 3.52 (s, 2H), 3.06−3.03 (m, 4H), 2.24 (s, 3H).

(5-Methyl-2-phenethyl-oxazol-4-yl)-acetic acid (5.05 g, 20.6 mmol) was reduced by the procedure described for **14a** and purified by column chromatography (500 mL SiO_2, 35% EtOAc/hexanes) to provide **14f** (3.99 g, 84%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.20 (m, 5H), 3.84 (q, J = 5.6 Hz, 2H), 3.06−2.67 (m, 4H), 2.62 (t, J = 5.6 Hz, 2H), 2.22 (s, 3H); MS m/z 232.19 $(M + H)^+$, 254.15 $(M + H + Na)^+$.

2-[5-Methyl-2-(3-phenyl-propyl)-oxazol-4-yl]-ethanol (14g). Hydrolysis of ester **13g** by the procedure described for **14a** provided [5-methyl-2-(3-phenyl-propyl)-oxazol-4-yl]-acetic acid, HPLC (98.5 area%, t_R = 7.6 min at 40% ISO), which was reduced by the procedure described for **14a** to provide **14g** as a clear oil following normal phase chromatography (90% for two steps). HPLC (98.4 area%, t_R = 8.2 min at 40% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 5 H), 3.85 (t, J = 5.71 Hz, 2 H), 3.14 (s, 1 H), 2.70 (td, J = 7.58, 1.98 Hz, 4 H), 2.62 (t, J = 5.49 Hz, 2 H), 2.21 (s, 3 H), 2.07 (q, J = 15.27, 7.58, 7.47 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.94, 143.01, 141.04, 131.48, 128.18, 128.06, 125.65, 61.48, 35.14, 28.51, 28.28, 27.48, 9.88.

2-(4-Hydroxy-phenoxy)-2-methyl-propionic Acid Ethyl Ester (16). A mixture of 2-(4-hydroxy-phenoxy)-2-methyl-propionic acid ethyl ester (22.42 g, 0.10 mol), 1,2-dibromoethane (100 mL), potassium carbonate (27.64 g, 0.20 mol), sodium sulfate (22.4 g), and 2B-3 ethanol (150 mL) was heated at reflux for 10 h and allowed to cool to room temperature. The mixture was filtered under vacuum, and the filter cake was rinsed with 2B-3 ethanol. Concentration of the filtrate under vacuum gave 33.25 g of oil. Purification by silica gel chromatography (MTBE/heptane eluent) yielded 27.79 g (83.9%) of **16**. HPLC (98.5 area%, t_R = 12.82 min, gradient method); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.88−6.77 (m, 4H), 4.25 (t, J = 5.3 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.76 (t, J = 5.3 Hz, 2H), 1.45 (s, 6H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.1, 153.3, 148.8, 121.2, 115.2, 79.1, 68.1, 60.8, 31.4, 24.9, 13.8; MS m/z 331.0 $(M + H)^+$.

2-Acetylamino-2-{2-[4-(1-ethoxycarbonyl-1-methyl-ethoxy)-phenoxy]-ethyl}-malonic Acid Diethyl Ester (19). To diethyl acetamidomalonate (12.0 g, 55.1 mmol) dissolved in DMF (120 mL) was added NaH (60% dispersion in mineral oil, 2.44 g, 61.1 mmol) at room temperature. The mixture was stirred for 90 min at ambient temperature. Then 2-[4-(2-bromoethoxy)-phenoxy]-2-methyl-propionic acid ethyl ester (18.0 g, 54.5 mmol) was added, and the reaction was heated to 70 °C overnight. The reaction was cooled to room temperature, diluted with water (150 mL), and extracted with diethyl ether. The combined organics were washed successively with water and then brine, dried, and concentrated to a yellow oil. The oil was triturated with hexanes and dried under vacuum to yield 22.7 g (89% yield) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 6.76 (m, 4H), 4.19−4.09 (m, 6H), 3.91 (t, J = 5.5 Hz, 2H), 2.57 (t, J = 5.5 Hz, 2H), 1.93 (s, 3H), 1.44 (s, 6H), 1.23−1.11 (m, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.2, 167.4, 153.5, 148.4, 121.3, 114.6, 79.1, 64.1, 62.7, 61.5, 60.8, 32.1, 24.8, 22.1, 13.9, 13.7; MS m/z 468.3 $(M + H)^+$, 466.4 $(M - H,)^-$.

2-Amino-4-[4-(1-carboxy-1-methyl-ethoxy)-phenoxy]-butyric Acid Hydrochloride Salt (20). Concentrated HCl (35.0 mL) was added to the triester **19** (13.6 g, 29.3 mmol); the mixture was heated to reflux for 6 h and then cooled to room temperature. The mixture was concentrated under vacuum, and the residue was diluted with acetonitrile (70 mL). Solids formed at room temperature and were filtered, rinsing with a small amount of acetonitrile to provide 7.60 g (78% yield) of the title compound. A second crop was obtained from the filtrate. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (br s, 3H), 6.83 (m, 4H), 4.09 (m, 2H), 4.00 (m, 1H), 2.27 (q, J = 6.2 Hz, 2H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.9, 170.5, 153.3, 148.9, 120.9, 115.0, 78.8, 63.5, 49.4, 29.6, 24.9; MS m/z 298.3 $(M + H)^+$. Anal. Calcd for $C_{14}H_{20}NO_6Cl$: C, 50.38; H, 6.04; N, 4.20. Found: C, 50.76; H, 6.08; N, 4.49.

2-[(Biphenyl-4-carbonyl)-amino]-4-[4-(1-carboxy-1-methyl-ethoxy)-phenoxy]-butyric Acid (21a). Amino diacid **20** (0.203 g, 0.94 mmol) and 4-biphenylcarbonyl chloride (0.316 g, 0.92 mmol) were dissolved in *N*-methylpyrrolidinone, and triethylamine (0.52 mL, 3.73 mmol) was added slowly. The mixture was stirred at room temperature for 2.5 h, diluted with water, and acidified with 1.0 N HCl. Product was extracted with EtOAc and dried. Removal of solvent under vacuum provided 0.403 g (92% yield) of the desired product, which was used without further purification. The product could be purified by crystallization from acetonitrile. HPLC (96.9 area%, t_R = 1.8 min at 80% ISO);^{1}H NMR (500 MHz, DMSO-d_6) δ 12.80 (br s, 2H), 8.75 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 6.83 (d, J = 9.2 Hz, 2H), 6.79 (d, J = 9.2 Hz, 2H), 4.63−4.58 (m, 1H), 4.06−4.00 (m, 2H), 3.34 (br s, 2H), 2.31−2.26 (m, 1H), 2.23−2.17 (m, 1H), 1.40 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.98, 173.40, 166.21, 153.63, 148.78, 142.86, 139.09, 132.66, 128.93, 128.05, 127.97, 126.79, 126.38, 120.92, 114.91, 78.79, 64.61,

49.72, 30.31, 24.89; HRMS−FAB *m/z* $[M + H]^+$ calcd for $C_{27}H_{28}NO_7$ 478.1866; found 478.1859.

4-[4-(1-Carboxy-1-methyl-ethoxy)-phenoxy]-2-[(4-phenyl-cyclohexanecarbonyl)-amino]-butyric Acid (21b). To a mixture of amino diacid **20** (0.600 g, 1.89 mmol) and triethylamine (0.63 mL, 4.49 mmol) in methylene chloride (4 mL) was slowly added 4-phenyl-cyclohexanecarbonyl chloride (0.420 g, 1.80 mmol) dissolved in methylene chloride (1 mL). After 30 min, the reaction mixture was partitioned between 1.0 N HCl (50 mL) and methylene chloride (50 mL). The organic phase was dried over sodium chloride and concentrated under reduced pressure to yield 869 mg (100%) of oil that was carried forward without further purification. HPLC (62.7 area%, t_R = 1.9 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.11 (m, 5H), 6.85 (d, J = 9.3 Hz, 2H), 6.72 (d, J = 9.3 Hz, 2H), 6.56 (d, J = 6.8 Hz, 2H), 4.73−4.68 (m, 1H), 4.11−3.97 (m, 2H), 2.49−2.42 (m, 2H), 2.37−2.33 (m, 2H), 2.23−2.08 (m, 2H), 2.02−1.92 (m, 4H), 1.61−1.51 (m, 2H), 1.49 (s, 6H), 1.47−1.41 (m, 2H).

2-(4-{3-[(Biphenyl-4-carbonyl)-amino]-4-oxo-pentyloxy}-phenoxy)-2-methyl-propionic Acid (22a). To compound **21a** (0.487 g, 1.02 mmol) dissolved in 2.2 mL pyridine was added 1.8 mL acetic anhydride, and the mixture was heated to 90 °C for 2 h. After cooling to room temperature the reaction was quenched with water (2.3 mL). This mixture was heated to 90 °C for 30 min, cooled to room temperature, and diluted with water, acidifying with 1.0 N HCl. Product was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried, and concentrated to a yellow oil. This product can be crystallized from toluene to provide **22a** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.88 (d, 1H, J = 7.3 Hz), 7.99 (d, 2H, J = 8.4 Hz), 7.80−7.72 (m, 4H), 7.52−7.38 (m, 3H), 6.82 (m, 4H), 4.59 (m, 1H), 4.02 (m, 2H), 2.29 (m, 1H), 2.17 (s, 3H), 2.11 (m, 1H), 1.42 (s, 6H). MS *m/z* 476.2 $(M + H)^+$, 474.3 $(M - H)^-$. Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.90; H, 6.13; N, 2.96.

2-(4-{3-[(Biphenyl-4-carbonyl)-amino]-4-oxo-heptyloxy}-phenoxy)-2-methyl-propionic Acid Methyl Ester (22b). Compound **21a** (0.676 g, 1.42 mmol), dissolved in pyridine (2.53 mL, 42.5 mmol), was treated with butyric anhydride (4.45 mL, 26.9 mmol) and heated at 90 °C for 1 h. Upon cooling to room temperature, 1 N HCl (50 mL) was added, and the mixture stirred for 1 h. The mixture was then extracted with ethyl acetate and concentrated under reduced pressure (27.4 area%, t_R = 2.3 min at 80% ISO). The acid dissolved in ethyl ether (50 mL) was treated with diazomethane, and then the reaction mixture was concentrated under reduced pressure and purified via SiO_2 chromatography to yield 535 mg (73%) of **22b** as an oil. HPLC (80.5 area%, t_R = 3.9 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.3 Hz, 2H), 7.68−7.61 (m, 4H), 7.48−7.37 (m, 3H), 6.80 (t, J = 8.8 Hz, 2H), 6.71 (t, J = 8.8 Hz, 2H), 4.90 (m, 1H), 4.07−3.97 (m, 1H), 3.77 (s, 3H), 2.78−2.70 (m, 1H) 2.63−2.55 (m, 2 H), 2.42−2.32 (m, 1H) 1.74−1.65 (m, 2H), 1.53 (s, 6H), 0.97 (t, J = 7.3 Hz, 3H).

2-(4-{3-[(Biphenyl-4-carbonyl)-amino]-4-oxo-4-phenyl-butoxy}-phenoxy)-2-methyl-propionic Acid Methyl Ester (22c). Compound **21a** (0.500 g, 1.05 mmol), dissolved in pyridine (3.4 mL, 41.9 mmol, 30 equiv), was treated with benzoic anhydride (0.711 g, 3.14 mmol, 3 equiv) and heated at 90 °C for 10 h. The reaction mixture was allowed to cool to room temperature and then partitioned by addition of 1.0 N HCl (50 mL) and methylene chloride (50 mL). The organic phase was dried over sodium chloride and concentrated under reduced pressure to 1.10 g of oil (85.5 area%, t_R = 2.4 min at 60% ISO). The acid (0.563 g, 1.05 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated with diazomethane. The reaction mixture was then concentrated under reduced pressure and purified via silica gel chromatography to yield 422 mg (73%) of **22c** as an oil. HPLC (88.8 area%, t_R = 4.0 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.59−7.33 (m, 7 H), 6.73 (d, J = 9.3 Hz, 2H), 6.64 (d, J = 9.3 Hz, 2H), 5.94−5.90 (m, 1H), 4.04−3.92 (m, 2H), 2.62−2.54 (m, 1H), 2.31−2.23 (m, 1H), 1.48 (m, 6H); MS *m/z* 552.3 $(M + H)^+$.

2-Methyl-2-(4-{4-oxo-3-[(4-phenyl-cyclohexanecarbonyl)-amino]-pentyloxy}-phenoxy)-propionic Acid Methyl Ester (22d). Acid **21b** (0.869 g, 1.80 mmol) was dissolved in pyridine (4.37 mL, 53.9 mmol, 30 equiv), treated with acetic anhydride (3.22 mL, 34.1 mmol, 19 equiv), and then heated at 90 °C for 3 h. After cooling to room temperature, the reaction mixture was treated with 5.0 N NaOH (7.5 mL). The mixture was partitioned after 10 min between ethyl ether (50 mL) and water (50 mL). The aqueous layer was then treated with sufficient 5.0 N HCl to achieve a pH of <3. The mixture was extracted with methylene chloride, and then the combined organic phases were dried over sodium chloride and concentrated under reduced pressure to an oil (73.1 area%, t_R = 2.2 min at 80% ISO). The acid (0.865 g, 1.80 mmol) was dissolved in ethyl ether (10 mL) and treated with diazomethane. The reaction mixture was then concentrated under reduced pressure and purified by silica gel chromatography to yield 368 mg (41%) of **22d** as an oil. HPLC (t_R = 2.9 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.23 (m, 2H), 7.17−7.12 (m, 3H), 6.76 (d, J = 9.3 Hz, 2H), 6.66 (d, J = 9.3 Hz, 2H), 6.56 (d, J = 6.3 Hz, 2H), 4.66−4.62 (m, 1H), 3.98−3.93 (m, 1H), 3.86−3.80 (m, 1H), 3.73 (s, 3H), 2.53−2.40 (m, 2H), 2.27 (s, 3H), 2.28−2.15 (m, 2H), 2.01−1.93 (m, 4H), 1.65−1.54 (m, 2H), 1.49 (s, 6H), 1.48−1.40 (m, 2H).

2-{4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic Acid (1a). Ketone **22a** (5.00 g, 10.51 mmol) was dissolved in 40 mL EtOAc. Acetic anhydride (3.22 g, 31.54 mmol) and 95−98% sulfuric acid (0.31 g, 3.16 mmol) in 2.5 mL EtOAc were added, and the mixture was heated at reflux for 3 h. The reaction mixture was cooled, and 5 N NaOH (12.6 mL, 63 mmol) diluted to 25 mL with water was added. The reaction was heated at reflux for 30 min and then cooled to room temperature. The resulting layers were separated. The organic layer was washed with 1 N HCl and 10% brine, dried (Na_2SO_4), concentrated in vacuo to 26.5 g, and stirred overnight at room temperature. The resulting slurry was diluted with heptane (24 mL) and cooled at 0 °C for 1 h. Filtration and drying yielded 4.21 g (88% yield) of **1a** in 95% yield as a white solid. Mp 141 −143.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.99 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 6.0 Hz, 2H), (d, J = 9.0 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H), 6.91−6.79 (m, 4H), 4.17 (t, J = 6.4 Hz, 2H), 2.92 (t, J = 6.4 Hz, 2H), 2.36 (s, 3H), 1.44 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.0, 158.1, 153.6, 148.8, 145.1, 141.4, 139.1, 132.8, 129.0, 127.9, 127.1, 126.6, 126.0, 121.0, 114.9, 78.9, 66.5, 25.7, 24.9; HRMS−FAB *m/z* $[M + H]^+$ calcd for $C_{28}H_{28}NO_5$ 458.1967; found 458.1958. Anal. Calcd for $C_{28}H_{27}NO_5$: C, 73.51; H, 5.95; N, 3.06. Found: C, 73.81; H, 6.16; N, 3.13.

2-{4-[2-(2-Biphenyl-4-yl-5-propyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic Acid (1b). Ester **22b** (0.514 g, 0.99 mmol) was dissolved in 6 mL of dry DMF followed by addition of phosphorus oxychloride (0.28 mL, 2.88 mmol, 3 equiv). The mixture was heated at 90 °C for 20 min under a nitrogen atmosphere, cooled to room temperature and treated with cold water (10 mL). The mixture was neutralized with 1.0 N sodium hydroxide and partitioned between ethyl ether (100 mL) and water (50 mL). The aqueous layer was back-extracted with ethyl ether, and the organic phases were combined, which were then washed with 5% aqueous LiCl, dried over NaCl, and concentrated in vacuo to yield an oil, which was immediately subjected to silica gel chromatography to yield 484 mg (98%) of an oil. HPLC (t_R = 12.7 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.3 Hz, 2H), 7.64−7.58 (m, 4H), 7.43−7.33 (m, 3H), 6.78−6.72 (m, 4H), 4.17 (t, J = 6.3 Hz, 2H), 3.73 (s, 3H), 2.94 (t, J = 6.3 Hz, 2H), 2.66 (t, J = 7.3 Hz, 2H), 1.73−1.67 (m, 2H), 1.48 (s, 6H), 0.97 (t, J = 7.3 Hz, 3H); MS *m/z* 500.1 $(M + H)^+$.

2-{4-[2-(2-Biphenyl-4-yl-5-propyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid methyl ester (0.484 g, 0.97

mmol) was dissolved in ethanol (5 mL) followed by addition of 5.0 N NaOH (2 mL). After 2 h at 50 °C for 2 h, the reaction mixture was allowed to cool to room temperature and then partitioned between methylene chloride (50 mL) and 1.0 N HCl (15 mL). The organic phase was separated, dried over sodium chloride, and concentrated in vacuo to yield 384 mg (82%) of **1b** as a glassy solid. HPLC (97.5 area%, t_R = 6.4 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.3 Hz, 2H), 7.63−7.58 (m, 4H), 7.43−7.33 (m, 3H), 6.86 (d, J = 9.3 Hz, 2H), 6.73 (d, J = 9.3 Hz, 2H), 4.13 (t, J = 6.3 Hz, 2H), 2.97 (t, J = 6.3 Hz, 2H), 2.66 (t, J = 7.3 Hz, 2H), 1.73−1.68 (m, 2H), 1.49 (s, 6H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 13.67, 21.78, 24.90, 26.05, 26.60, 66.95, 80.14, 114.86, 122.36, 126.05, 126.57, 127.01, 127.34, 127.76, 128.82, 132.34, 140.13, 142.77, 147.89, 149.24, 154.97, 159.57, 176.47; HRMS−FAB m/z $[M + H]^+$ calcd for $C_{30}H_{31}NO_5$ 486.2280, found 486.2308.

2-{4-[2-(2-Biphenyl-4-yl-5-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic Acid (1c). Cyclodehydration of ester **22c** (0.422 g, 0.765 mmol) was carried out by the procedure described for **1b** to yield 362 mg (89%) of an oil. HPLC (88.8 area%, t_R = 13.8 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8. Hz, 2H), 7.47−7.33 (m, 6H), 6.75 (m, 4H), 4.36 (t, J = 6.8 Hz, 2H), 3.72 (s, 3H), 3.29 (t, J = 6.8 Hz, 2H), 1.48 (s, 6H).

Hydrolysis of 2-{4-[2-(2-biphenyl-4-yl-5-phenyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid methyl ester (0.360 g, 0.675 mmol) was carried out by the procedure described for **1b** to yield 347 mg (99%) of **1c** a glassy solid. HPLC (92.4 area%, t_R = 7.2 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.46−7.34 (m, 6H), 6.87 (d, J = 9.3 Hz, 2H), 6.76 (d, J = 9.3 Hz, 2H), 4.32 (t, J = 6.8 Hz, 2H), 3.29 (t, J = 6.8 Hz, 2H), 1.50 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 24.88, 27.40, 66.86, 80.32, 115.07, 122.71, 125.70, 126.04, 126.96, 127.11, 127.50, 127.94, 128.37, 128.53, 128.88, 128.92, 133.56, 140.10, 143.31, 147.20, 147.76, 155.14, 159.89, 176.61; HRMS−FAB m/z $[M + H]^+$ calcd for $C_{33}H_{29}NO_5$, 520.2124; found 520.2107.

2-Methyl-2-(4-{2-[5-methyl-2-(4-phenyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenoxy)-propionic Acid (1d). Cyclodehydration of ester **22d** (0.422 g, 0.765 mmol) was carried out by the procedure described for **1b** to yield 327 mg (92%) of an oil. HPLC (97.5 area%, t_R = 7.2 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.13 (m, 5H), 6.77−6.70 (m, 4H), 4.08 (t, J = 6.8 Hz, 2H), 3.73 (s, 3H), 2.87 (t, J = 6.8 Hz, 2H), 2.83−2.76 (m, 1H), 2.55−2.47 (m, 1H), 2.22 (s, 3H), 2.17−2.13 (m, 2H), 1.98−1.94 (m, 2H), 1.72−1.62 (m, 2H), 1.56−1.49 (m, 2H), 1.47 (s, 6H).

Hydrolysis of 2-methyl-2-(4-{2-[5-methyl-2-(4-phenyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenoxy)-propionic acid methyl ester (0.322 g, 0.67 mmol) was carried out by the procedure described for **1b** to yield 312 mg (100%) of **1d** as a glassy solid. HPLC (96.7 area%, t_R = 4.0 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.11 (m, 5H), 6.82 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 4.04 (t, J = 6.8 Hz, 2H), 2.89−2.76 (m, 3H), 2.54−2.47 (m, 1H), 2.22 (s, 3H), 2.17−2.13 (m, 2H), 1.98−1.95 (m, 2H), 1.72−1.62 (m, 2H), 1.56−1.49 (m, 2H), 1.47 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 10.02, 25.05, 25.41, 30.60, 33.34, 37.05, 43.45, 66.70, 80.01, 114.90, 122.01, 126.17, 126.76, 128.42, 129.29, 145.07, 146.64, 148.36, 154.63, 166.43, 176.48; HRMS−FAB m/z $[M + H]^+$ calcd for $C_{28}H_{33}NO_5$ 464.2437, found 464.2435.

2-Benzylamino-4-[4-(1-ethoxycarbonyl-1-methyl-ethoxy)-phenoxy]-butyric Acid Ethyl Ester (24). Amino-4-[4-(1-ethoxycarbonyl-1-methyl-ethoxy)-phenoxy]-butyric acid ethyl ester (0.612 g, 1.73 mmol) and benzaldehyde (220 mg, 2.08 mmol) were dissolved in 10 mL of methylene chloride followed by addition of sodium triacetoxyborohydride (550 mg, 2.60 mmol). After 4 h at room temperature, the reaction mixture was partitioned between methylene chloride (50 mL) and 0.1 N HCl (50 mL). The pH of the mixture was then adjusted to ∼13 with 1.0 N NaOH, the layers were separated, and the aqueous layer was extracted with methylene chloride. The combined organic phases were dried over sodium chloride and then concentrated under reduced pressure. The crude product was purified by silica gel chromatography to yield **24** (492 mg, 64%) as an oil. HPLC (t_R = 2.8 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.18 (m, 5H), 6.79−6.76 (m, 2H), 6.70−6.68 (m, 2 H), 4.22−4.12 (m, 4H), 4.08−4.02 (m, 1H), 3.99−3.91 (m, 1H), 3.83−3.80 (d, J = 12.7 Hz, 1H), 3.65−3.62 (d, J = 12.7 Hz, 1H), 3.49−3.47 (m, 1H), 2.17−2.09 (m, 1 H), 2.00−1.92 (m, 1H), 1.49 (s, 6H), 1.26−1.20 (m, 6H).

2-[Benzyl-(biphenyl-4-carbonyl)-amino]-4-[4-(1-ethoxycarbonyl-1-methyl-ethoxy)-phenoxy]-butyric Acid Ethyl Ester (25). Diester **24** (0.490 g, 1.10 mmol) was dissolved in 10 mL of methylene chloride followed by addition of triethylamine (0.31 mL, 2.21 mmol) and biphenyl-4-carbonyl chloride (0.287 g, 1.33 mmol). After 12 h at room temperature, the reaction mixture was partitioned between methylene chloride (50 mL) and 0.1 N HCl (50 mL). The organic phase was dried over sodium chloride and then concentrated under reduced pressure to yield 687 mg (100%) of **25** as an oil. HPLC (91.6 area%, t_R = 7.6 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.20 (m, 14H), 6.77−6.46 (m, 4H), 4.91−4.45 (m, 2H), 4.19−3.66 (m, 7H), 2.78−2.12 (m, 2H), 1.49 (s, 6H), 1.25−1.22 (m, 6H).

2-{4-[2-(2-Biphenyl-4-yl-5-trifluoromethyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic Acid (1e). Compound **25** (0.687 g, 1.10 mmol) was dissolved in 5 mL of dioxane followed by addition of 5.0 N NaOH (2.3 mL, 11.6 mmol). The mixture was heated at 60 °C for 7 h. The reaction mixture was allowed to cool to room temperature followed by addition of 1.0 N HCl (12 mL, 12 mmol) and then partitioned by addition of methylene chloride (50 mL). The organic phase was separated, dried over sodium chloride, and concentrated under reduced pressure to yield 690 mg (∼100%) of a glassy solid. HPLC (94.9 area%, t_R = 2.2 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.82 (broad s, 2H), 7.70−7.75 (m, 4H), 7.45−7.17 (m, 10H), 6.75−6.48 (m, 4H), 2.24−2.00 (m, 2H), 1.39 (s, 6H); MS m/z 568.31 $(M + H)^+$.

A sample of 2-[benzyl-(biphenyl-4-carbonyl)-amino]-4-[4-(1-carboxy-1-methyl-ethoxy)-phenoxy]-butyric acid (0.625 g, 1.10 mmol) was dissolved in 5 mL of toluene followed by addition of pyridine (0.54 mL, 6.61 mmol, 6 equiv). The reaction mixture was chilled to 0 °C, and trifluoroacetic anhydride (0.47 mL, 3.30 mmol, 3 equiv) was then added. The reaction mixture was allowed to stir at room temperature for 12 h followed by heating at reflux for 9 h. The reaction mixture was then allowed to cool to room temperature followed by partitioning between water (50 mL) and methylene chloride (50 mL). The organic phase was dried over sodium chloride and concentrated under reduced pressure to yield 563 mg of a glassy solid. The material was treated with diazomethane and then concentrated to an oil under reduced pressure prior to silica gel chromatography to yield 141 mg (25%) of an oil. HPLC (96.2 area%, t_R = 11.7 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.45−7.41 (m, 2H), 7.37−7.34 (m, 1H), 6.78−6.73 (m, 4H), 4.22 (t, J = 6.8 Hz, 2H), 3.72 (s, 3H), 3.14 (t, J = 6.8 Hz, 2H), 1.48 (s, 6H); MS m/z 526.3 $(M + H)^+$.

2-{4-[2-(2-Biphenyl-4-yl-5-trifluoromethyl-oxazol-4-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid methyl ester (141 mg, 0.21 mmol) was dissolved in ethanol (2 mL) followed by addition of 5.0 N NaOH (0.6 mL). After 1 h at 50 °C, the reaction mixture was cooled to room temperature, acidified with 1.0 N HCl (3 mL), and then extracted with methylene chloride. The organic phase was dried over sodium chloride and concentrated under reduced pressure to yield 134 mg (98%, 24% overall) of a glassy solid. HPLC (>99.9 area%, t_R = 5.8 min at 80% ISO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.45−7.36 (m, 3H), 6.86 (d, J = 9.3 Hz, 2H), 6.78 (d, J = 9.3 Hz, 2H), 4.24 (t, J = 6.3 Hz, 2H), 3.15 (t, J = 6.3 Hz, 2H), 1.48 (s, 6H); ^{13}C NMR ($CDCl_3$) δ

24.75, 26.55, 29.65, 65.83, 80.39, 115.06, 122.95, 124.72, 127.09, 127.45, 127.52, 128.11, 128.91, 139.78, 140.08, 140.11, 144.32, 147.53, 155.08, 162.07, 176.68; HRMS−FAB *m/z* $[M + H]^+$ calcd for $C_{28}H_{24}F_3NO_5$, 512.1685; found 512.1709.

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Supporting Information Available: Experimental procedures and spectral data for intermediates **11a**−**f** and **23** and the ^{1}H NMR spectra for compounds **11f**, **12a,c,d,f**, **13a,c**, **14d,f**, **21a**, **22b**−**d**, **1b**−**e**, and **23**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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