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Noncovalent Inhibitors of Human Leukocyte Elastase Based on the 4-Imidazolidinone Scaffold

Liuqing Wei, Xiangdong Gan, Jiaying Zhong, Kevin R. Alliston and William C. Groutas*

Department of Chemistry, Wichita State University, Wichita, KS 67260, USA

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Abstract—A central problem associated with the design of enzyme inhibitors in general, and serine protease inhibitors in particular, is the identification of templates capable of binding to the active site of an enzyme in a predictable and substrate-like fashion, orienting appended recognition elements in a correct spatial relationship so that favorable binding interactions with multiple sites are achieved. Described herein for the first time is the design of noncovalent inhibitors of human leukocyte elastase that employs a functionalized 4-imidazolidinone scaffold.

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Introduction

Proteases of mammalian, viral, bacterial and parasitic origin are directly involved or have been implicated in the pathogenesis of a range of human diseases,^{1,2} consequently, mammalian and non-mammalian serine, cysteine, aspartic and metallo-proteases have been the subject of intense investigation in recent years.³ The development of agents capable of modulating the activity of proteases may lead to the emergence of new therapeutic interventions.

In recent studies we have described the structure-based design of a novel heterocyclic scaffold and its use in the mechanism-based inactivation of (chymo)trypsin-like serine proteases.^{4–8} We have furthermore demonstrated that the 1,2,5-thiadiazolidin-3-one 1,1 dioxide scaffold (Ia) (Fig. 1) is a versatile core structure that can be used in (a) the design of covalent and noncovalent inhibitors of serine proteases and to fashion inhibitors that show *absolute* selectivity between neutral, basic and acidic serine proteases; (b) is amenable to the construction of libraries for lead identification and optimization and, (c) makes possible the attachment and optimal spatial orientation of recognition elements, thereby allowing the exploitation of favorable binding interactions with both the S and S' subsites of a target protease.

Inhibitor design

Based on the results of preliminary computational and modeling studies, as well as insights gained from the aforementioned studies with the 1,2,5-thiadiazolidin-3-one 1,1 dioxide scaffold, we hypothesized that appending recognition elements P₁, R₂ and R₃ to a planar or near planar cyclic system in a way that these elements bear the same vector relationship as when similarly appended to the 1,2,5-thiadiazolidin-3-one 1,1 dioxide scaffold would yield a series of heterocyclic scaffolds [represented by structure (I)] capable of binding to the active site of (chymo)trypsin-like serine proteases, leading to inhibition of these enzymes. The evolution of the design process is summarized in Figure 1. Described herein are the results of preliminary studies related to the use of substituted 4-imidazolidinones (Ib) in the inhibition of human leukocyte elastase that lend support to the aforementioned hypothesis, as well as pave the way toward placing the design of protease inhibitors on a more secure structural and biochemical footing.

Chemistry

Compounds 6–16 were synthesized as illustrated in Scheme 1 and are listed in Tables 1 and 2. As indicated in Scheme 1, the amino acid derivative selected to serve as the starting material is dictated by the primary substrate specificity of the target protease. Likewise, the nature of R₂ and R₃ was chosen on the basis of what is known about the active site subsites of HLE (vide

*Corresponding author. Tel.: +1-316-978-7374; fax: +1-316-978-3431; e-mail: bill.groutas@wichita.edu

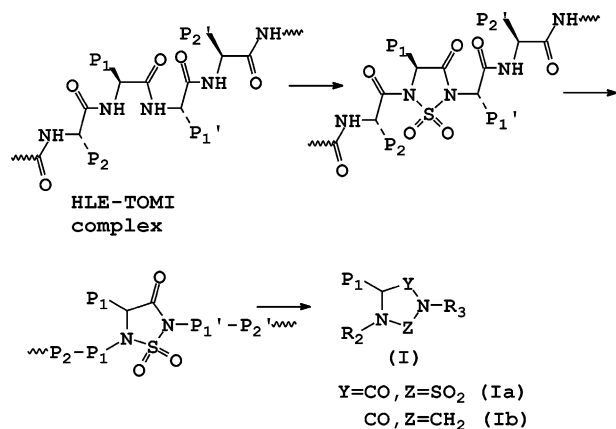
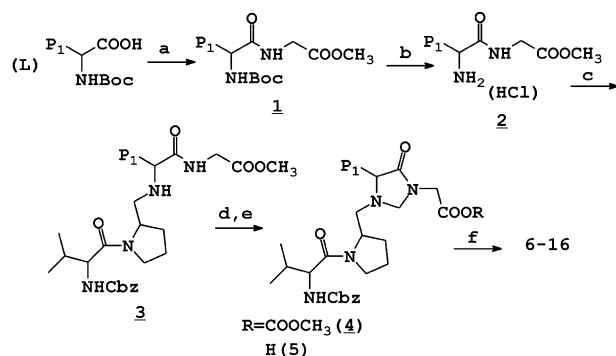


Figure 1. Evolution of the design of inhibitor (I) beginning with the human leukocyte elastase–turkey ovomucoid inhibitor (HLE–TOMI) complex.



Scheme 1. (a) IBCF/NMM then Gly-OCH₃ (HCl); (b) HCl/dioxane; (c) Cbz-L-Val-L-prolinal/NaBH (OAc)₃; (d) 37% aq HCHO; (e) aq KOH; (f) CDI/THF then RNH₂.

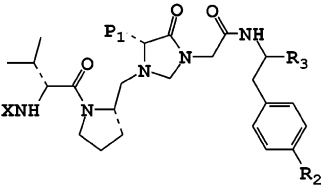
infra). A representative synthesis is described in the Experimental.

Biochemical Studies

The inhibitory activity of compounds **6–16** was evaluated by determining the K_i using Dixon plots⁹ and the results are listed in Table 3. A representative experiment was carried out according to the following procedure: to a thermostatted solution of 930 μ L 0.1 M HEPES buffer containing 0.5 M NaCl, pH 7.25, was added DMSO (50 μ L), human leukocyte elastase (10 μ L solution in 0.05 M sodium acetate buffer containing 0.5 M NaCl, pH 5.5, for a final enzyme concentration of 70 nM) and, lastly, 10 μ L methoxysuccinyl-Ala-Ala-Pro-Val *p*-nitroanilide in DMSO for a final substrate concentration of 0.70 mM, and the rate of hydrolysis was determined by monitoring the absorbance at 410 nm for 2 min. The experiment was repeated in the presence of varying amounts of inhibitor **11** (10–50 μ L) at a constant final concentration of DMSO (5%), and the rates of substrate hydrolysis determined.

The series of experiments described above was repeated at two additional substrate concentrations (final sub-

Table 1. Structures of compounds **6–16**

	
X =	Cbz, P ₁ = isobutyl, R ₂ = H, R ₃ = COOt-Bu, (6)
	Cbz, P ₁ = isobutyl, R ₂ = H, R ₃ = COOCH ₃ , L-isomer (7)
	Cbz, P ₁ = isobutyl, R ₂ = H, R ₃ = COOCH ₃ , D-isomer (8)
	Cbz, P ₁ = isobutyl, R ₂ = H, R ₃ = COOH (9)
	Cbz, P ₁ = isobutyl, R ₂ = OH, R ₃ = COOCH ₃ (10)
	Cbz, P ₁ = isobutyl, R ₂ = R ₃ = H (11)
	H, P ₁ = isobutyl, R ₂ = R ₃ = H (12)
	CH ₃ SO ₂ , P ₁ = isobutyl, R ₂ = R ₃ = H (13)
	CH ₃ CH ₂ OCO, P ₁ = isobutyl, R ₂ = R ₃ = H (14)
	Cbz, P ₁ = isobutyl, R ₂ = R ₃ = H (15)
	Cbz, P ₁ = isobutyl, R ₂ = H, R ₃ = COOCH ₃ , L-isomer (16)

strate concentrations: 2.3315×10^{-4} M and 1.1658×10^{-4} M). All rates were determined in triplicate. The inverse of the average velocities was plotted against the final inhibitor concentrations and the K_i determined from the intersection of the three lines (each $R^2 > 0.99$). A representative $1/v$ versus $[I]$ plot is shown in Figure 2.

Results and Discussion

The rational and successful development of protease inhibitors that exhibit high enzyme selectivity and potency is largely dependent on the design of highly functionalized templates that are capable of exploiting subtle differences in the topography of the active sites of the target enzymes. This is of particular importance in the case of proteases which have the *same or very similar* primary substrate specificity such as, for example, the serine proteases of the coagulation cascade (thrombin, factor Xa, plasmin, etc.), or the neutrophil-derived enzymes human leukocyte elastase (HLE) and proteinase 3 (PR 3). In such cases, attainment of maximal enzyme selectivity is possible only if subtle structural differences in the subsites on either side of the scissile bond can be exploited. Accomplishing this requires the availability of templates that are capable of docking to the active site in a predictable and substrate-like fashion, at the same time orienting appended binding elements toward the S₂–S_n and S' subsites.¹⁰ Exploitation of differences in the S and S' subsites can then be achieved by structural modification of the appended recognition elements.

HLE, a neutrophil-derived serine protease that has been implicated in inflammatory diseases^{11,12} and cancer metastasis,^{13,14} was chosen as a representative serine protease for exploring the aforementioned ideas. HLE is known to interact with its substrate through a series of hydrogen bonds and hydrophobic binding interactions, as illustrated in Figure 3.¹⁵

Based on earlier structure–activity relationship studies with the 1,2,5-thiadiazolidin-3-one 1,1 dioxide scaffold, as well as modeling and computational studies, we specu-

Table 2. Spectral data of inhibitors 6–16

Compd	¹ H NMR Data (δ)	MF (anal.)	M _r
6	(CDCl ₃) 0.85–1.00 (m, 12H), 1.32–1.58 (m, 12H), 1.75–2.00 (m, 6H), 2.39–2.42 (m, 1H), 2.76–2.90 (m, 1H), 3.02–3.18 (m, 3H), 3.40–3.58 (m, 1H), 3.63–3.72 (m, 1H), 3.80–3.98 (m, 3H), 4.16–4.25 (m, 1H), 4.26–4.37 (m, 1H), 4.52–4.56 (d, 1H), 4.67–4.74 (m, 1H), 5.00–5.18 (m, 2H), 5.58–5.63 (d, 1H), 6.43–6.48 (d, 1H), 7.10–7.40 (m, 10H)	C ₄₀ H ₅₇ N ₅ O ₇	719.91
7	(CDCl ₃) 0.82–1.04 (m, 12H), 1.35–1.45 (m, 1H), 1.47–1.59 (m, 1H), 1.64–2.02 (m, 6H), 2.35–2.42 (m, 1H), 2.72–2.90 (m, 1H), 3.02–3.20 (m, 3H), 3.40–3.52 (m, 1H), 3.63–3.74 (m, 4H), 3.80–3.97 (m, 3H), 4.20–4.26 (m, 1H), 4.27–4.37 (m, 1H), 4.52–4.56 (d, 1H), 4.78–4.86 (m, 1H), 5.04–5.14 (m, 2H), 5.52–5.63 (d, 1H), 6.52–6.60 (d, 1H), 7.05–7.40 (m, 10H)	C ₃₇ H ₅₁ N ₅ O ₇	677.83
8	(CDCl ₃) 0.82–1.04 (m, 12H), 1.35–1.45 (m, 1H), 1.47–1.59 (m, 1H), 1.64–2.02 (m, 6H), 2.35–2.42 (m, 1H), 2.72–2.90 (m, 1H), 3.02–3.20 (m, 3H), 3.40–3.52 (m, 1H), 3.63–3.74 (m, 4H), 3.75–3.81 (m, 1H), 3.90–4.05 (m, 2H), 4.23–4.35 (m, 2H), 4.52–4.56 (d, 1H), 4.78–4.86 (m, 1H), 5.04–5.14 (m, 2H), 5.52–5.63 (d, 1H), 6.52–6.60 (d, 1H), 7.05–7.40 (m, 10H)	C ₃₇ H ₅₁ N ₅ O ₇	677.83
9	(CDCl ₃) 0.81–1.00 (m, 12H), 1.32–1.37 (s, 1H), 1.56–1.72 (br m, 2H), 1.74–2.08 (m, 6H), 2.45–2.52 (s, 1H), 2.85–3.01 (m, 1H), 3.02–3.16 (m, 2H), 3.18–3.40 (br m, 1H), 3.43–3.60 (m, 1H), 3.63–3.80 (m, 1H), 3.83–3.95 (m, 2H), 3.95–4.07 (m, 1H), 4.09–4.20 (m, 1H), 4.37–4.50 (m, 2H), 4.72–4.83 (m, 1H), 4.97–5.14 (m, 2H), 7.15–7.42 (m, 10H), 7.50–7.63 (d, 1H), 8.54–8.60 (s, 1H)	C ₃₆ H ₅₀ ClN ₅ O ₇	700.26
10	(CDCl ₃) 0.84–1.06 (m, 12H), 1.34–1.45 (m, 1H), 1.47–1.57 (m, 1H), 1.77–2.00 (m, 6H), 2.35–2.43 (m, 1H), 2.78–2.91 (m, 1H), 2.95–3.16 (m, 2H), 3.18–3.23 (m, 1H), 3.48–3.60 (m, 2H), 3.72–3.80 (m, 4H), 3.83–4.13 (m, 2H), 4.18–4.32 (m, 2H), 4.36–4.42 (m, 1H), 4.75–4.83 (m, 1H), 5.02–5.18 (m, 2H), 5.55–5.63 (m, 1H), 6.54–6.57 (d, 1H), 6.70–7.40 (m, 9H)	C ₃₇ H ₅₁ N ₅ O ₈	693.83
11	(CDCl ₃) 0.82–1.04 (m, 12H), 1.33–1.45 (m, 1H), 1.53–1.60 (m, 1H), 1.70–2.02 (m, 6H), 2.34–2.43 (m, 1H), 2.72–2.93 (m, 3H), 3.10–3.19 (t, 1H), 3.37–3.62 (m, 3H), 3.63–3.80 (m, 1H), 3.80–4.02 (m, 3H), 4.12–4.38 (m, 2H), 4.52–4.62 (m, 1H), 5.08–5.15 (m, 2H), 5.44–5.53 (m, 1H), 6.12–6.22 (m, 1H), 6.95–7.42 (m, 10H)	C ₃₅ H ₄₉ N ₅ O ₅	619.79
12	(CDCl ₃) 0.82–1.04 (m, 12H), 1.30–1.45 (m, 1H), 1.47–1.60 (m, 1H), 1.60–2.01 (m, 8H), 2.37–2.43 (m, 1H), 2.72–2.92 (m, 3H), 3.10–3.19 (t, 1H), 3.24–3.33 (d, 1H), 3.36–4.00 (m, 4H), 3.80–4.00 (m, 3H), 4.20–4.33 (m, 1H), 4.52–4.58 (m, 1H), 6.24–6.32 (m, 1H), 7.09–7.36 (m, 5H)	C ₂₇ H ₄₃ N ₅ O ₃	485.66
13	(CDCl ₃) 0.80–1.04 (m, 12H), 1.30–1.42 (m, 1H), 1.42–1.60 (m, 1H), 1.73–2.00 (m, 6H), 2.37–2.43 (m, 1H), 2.70–2.88 (m, 6H), 3.10–3.19 (t, 1H), 3.35–3.65 (m, 4H), 3.67–3.80 (m, 1H), 3.80–3.97 (m, 3H), 4.17–4.33 (m, 1H), 4.52–4.58 (m, 1H), 5.43–5.56 (m, 1H), 6.30–6.40 (m, 1H), 7.09–7.32 (m, 5H)	C ₂₈ H ₄₅ N ₅ O ₅ S	563.75
14	(CDCl ₃) 0.65–0.96 (m, 12H), 1.05–1.25 (m, 3H), 1.26–1.38 (m, 1H), 1.40–1.56 (m, 1H), 1.73–1.87 (m, 6H), 2.30–2.43 (m, 1H), 2.64–2.82 (m, 3H), 3.00–3.15 (t, 1H), 3.24–3.55 (m, 3H), 3.60–3.67 (m, 1H), 3.68–3.80 (m, 1H), 3.82–3.94 (m, 2H), 3.95–4.08 (m, 2H), 4.13–4.26 (m, 2H), 4.42–4.53 (m, 1H), 5.33–5.40 (d, 1H), 6.18–6.23 (m, 1H), 7.00–7.26 (m, 5H)	C ₃₀ H ₄₇ N ₅ O ₅	557.72
15	(CDCl ₃) 0.78–1.05 (m, 12H), 1.70–2.06 (m, 6H), 2.40–2.64 (m, 1H), 2.72–2.90 (m, 2H), 1.92–3.00 (m, 1H), 3.04–3.16 (m, 1H), 3.38–3.62 (m, 3H), 3.63–3.75 (m, 1H), 3.77–3.90 (m, 2H), 3.91–4.04 (m, 1H), 4.12–4.22 (m, 1H), 4.25–4.35 (m, 1H), 4.45–4.50 (m, 1H), 4.96–5.15 (m, 2H), 5.50–5.63 (m, 1H), 6.30–6.40 (m, 1H), 7.07–7.40 (m, 10H)	C ₃₄ H ₄₇ N ₅ O ₅	605.77
16	(CDCl ₃) 0.82–1.04 (m, 12H), 1.80–2.04 (m, 6H), 2.35–2.50 (m, 1H), 2.80–3.00 (m, 1H), 3.02–3.20 (m, 3H), 3.42–3.52 (m, 1H), 3.63–3.75 (m, 4H), 3.80–4.00 (m, 3H), 4.15–4.22 (m, 1H), 4.27–4.37 (m, 1H), 4.52–4.56 (d, 1H), 4.79–4.87 (m, 1H), 5.02–5.12 (m, 2H), 5.52–5.60 (d, 1H), 6.56–6.60 (d, 1H), 7.05–7.40 (m, 10H)	C ₃₆ H ₄₉ N ₅ O ₇	663.8

Table 3. Inhibitory activity of compounds **6–16** toward human leukocyte elastase

Compd	K _i (μM)
6	65.0
7	18.0
8	40.0
9	70.0
10	40.0
11	12.0
12	Inactive
13	Inactive
14	Inactive
15	9.0
16	22.0

lated that derivatives based on the 4-imidazolidinone template may exhibit inhibitory activity toward HLE and related (chymo)trypsin-like proteases. Since many of the known inhibitors of HLE such as, for example, peptidyl trifluoromethylketones and related transition state inhibitors,^{16,17} incorporate in their structures a -Val-Pro- segment that interacts with the S₃ and S₂ subsites, we decided to attach this sequence to the heterocyclic template. An aromatic amino acid was also attached to the inhibitor in order to exploit favorable binding interactions with Phe-41, located near the S'₂ subsite.

The results summarized in Table 2 clearly show that the 4-imidazolidinone template can be used in the design of

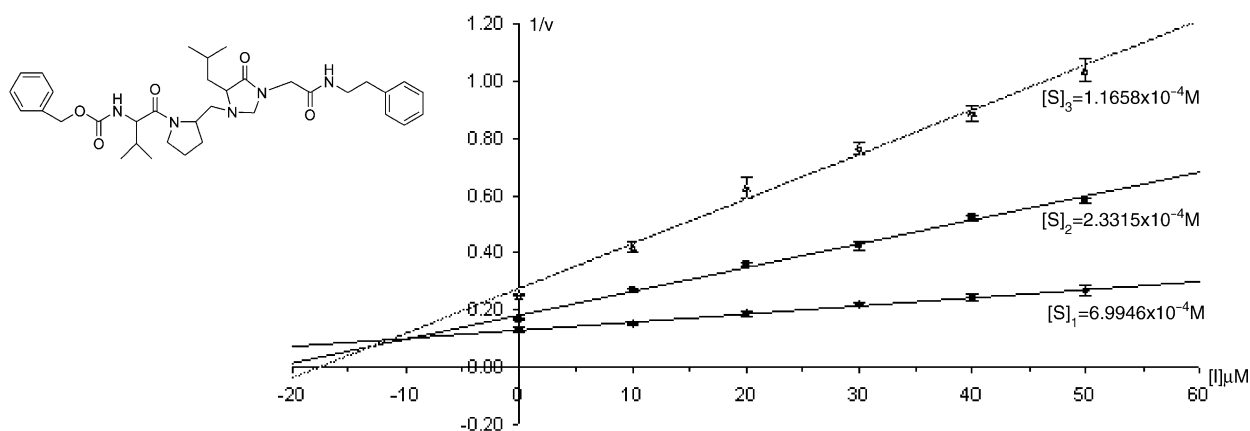


Figure 2. Dixon plot showing the inhibition of human leukocyte elastase by compound **11**.

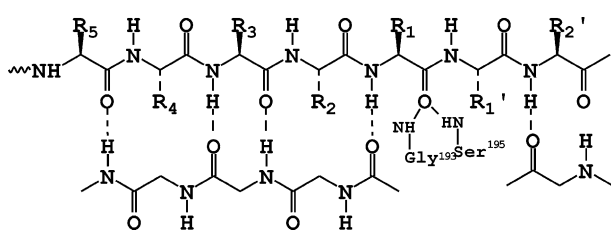


Figure 3. Main-chain and side-chain binding interactions between a substrate or inhibitor and the active site of HLE.

inhibitors of human leukocyte elastase. While the potency of many of the compounds was modest, many of the compounds did possess inhibitory activity toward HLE. Compounds **11** and **15** (Table 2), having a phenethylamine moiety oriented toward the S' subsites and differing only in the nature of the primary specificity residue (P_1 =isobutyl and isopropyl, respectively), were found to have the highest potency (K_i 12.0 and 9.0 μ M, respectively). Interestingly, removal and/or replacement of the Cbz group resulted in total loss of inhibitory activity (Table 2, compounds **12–14**). Replacement of 2-phenethylamine with (L) phenylalanine methyl ester yielded **7** which was near equipotent to compound **11**. Potency decreased 2-fold when (D) phenylalanine methyl ester was attached at the same position.

In summary, these studies have demonstrated that derivatives based on the 4-imidazolidinone scaffold function as inhibitors of HLE and, possibly, related serine proteases. Furthermore, the results of these studies, as well as related studies in progress,¹⁸ provide tentative support to the hypothesis that surrogate scaffolds with appended recognition elements oriented in space the same way as when appended to the 1,2,5-thiadiazolidin-3-one 1,1 dioxide scaffold, exhibit protease inhibitory activity.

Experimental

General

Melting points were recorded on a Mel-Temp apparatus and are uncorrected. The ¹H and ¹³C NMR spectra of

the synthesized compounds were recorded on a Varian XL-300 or XL-400 spectrometer. The synthesized compounds were purified using flash chromatography. A Hewlett-Packard diode array UV/VIS spectrophotometer was used in the enzyme assays and inhibition studies. Human leukocyte elastase was purchased from Elastin Products Co., Owensville, MO, USA. Methoxysuccinyl Ala-Ala-Pro-Val *p*-nitroanilide was purchased from Sigma Chemicals Co., St. Louis, MO, USA. 2M oxalyl chloride in methylene chloride was purchased from Aldrich Chemical Co.

Synthesis of compound 1. A solution of Boc-L-leucine (40 g; 173 mmol) in dry THF (600 mL) was cooled in an ice-bath and then treated with *N*-methylmorpholine (NMM) (87.6 g; 0.80 mol). Isobutyl chloroformate (23.6 g; 173 mmol) was added and, after stirring the reaction mixture for 5 min, glycine methyl ester hydrochloride (21.6 g; 173 mmol) was added. The ice bath was removed and the reaction mixture was stirred for 1 h. The solvent was removed using a rotary evaporator and the residue was treated with ethyl acetate (600 mL). The resulting solution was washed with 5% aq HCl (200 mL), 5% aq NaHCO₃ (200 mL) and brine (200 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent removed in vacuo. Evaporation of the solvent left a crude solid which was purified by recrystallization to yield a white solid (36.36 g; 70% yield), mp 123–124 °C. ¹H NMR (CDCl₃) δ 0.91–0.96 (m, 6H), 1.50–1.55 (m, 1H), 1.63–1.73 (dd, 2H), 3.75 (s, 3H), 4.04–4.06 (d, 2H), 4.14–4.24 (br s, 1H), 4.98–5.02 (d, 2H), 6.75–6.80 (br s, 1H).

Synthesis of compound 2. A solution of **1** (33.86 g; 112 mmol) in dry dioxane (154 mL) was treated with dry hydrogen chloride (280 mL 4.0 M HCl in dioxane) dropwise. After stirring for 3 h, the solvent was removed on the rotovac and the residue washed with ethyl ether (3 $\times$ 200 mL). Residual ethyl ether was removed in vacuum, yielding a light-yellow hygroscopic foam (32.70 g; 100% yield) that was used in the next step without further purification. ¹H NMR (acetone-*d*₆) δ 0.98–1.10 (m, 6H), 1.78–1.94 (m, 2H), 1.95–2.02 (m, 1H), 3.74–3.78 (s, 3H), 4.02–4.12 (d, 2H), 4.41–4.46 (t, 1H), 8.18–8.23 (br s, 2H), 8.60–8.66 (br s, 1H).

Synthesis of compound 3. To a solution of 2 M oxalyl chloride in methylene chloride (32 mL; 61 mmol) cooled to -78°C under nitrogen was added dropwise a solution of dry dimethyl sulfoxide (6.8 mL; 90 mmol) in dry methylene chloride (50 mL) over 5 min. After the mixture was stirred for 0.5 h, a solution of Cbz-L-Val-L-prolinol (14 g; 42 mmol) in dry methylene chloride (100 mL) was added dropwise. After stirring for 40 min, dry triethylamine (13.00 g; 128 mmol) in dry methylene chloride (50 mL) was added to the reaction mixture and stirring continued for 15 min. Glacial acetic acid (8.20 g; 139 mmol) was added, followed by sodium (triacetoxo) borohydride (14.0 g; 59 mmol) and compound 2. The reaction mixture was stirred for 4 h and then neutralized by adding dropwise cold 10% aq NaOH (pH $\sim$ 10). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3×300 mL). Removal of the solvent left a crude product which was purified by flash chromatography (silica gel/hexane/ethyl acetate) to yield a light-yellow oil (12.7 g; 58% yield). ^1H NMR δ 0.84–1.02 (m, 12H), 1.30–1.43 (m, 1H), 1.44–1.60 (m, 1H), 1.60–1.68 (m, 1H), 1.91–2.02 (m, 6H), 2.42–2.55 (m, 1H), 2.76–2.85 (m, 1H), 3.06–3.16 (m, 1H), 3.44–3.56 (m, 1H), 3.73–3.78 (s, 3H), 3.83–3.95 (dd, 1H), 4.12–4.24 (dd, 1H), 4.25–4.38 (t, 1H), 5.10–5.13 (s, 2H), 5.46–5.64 (m, 1H), 7.25–7.42 (m, 5H), 7.72–8.86 (br m, 1H).

Synthesis of compound 4. A mixture of 3 (11.70 g; 22.5 mmol) and 37% aq formaldehyde (24 mL) was refluxed for 0.5 h. The reaction mixture was allowed to cool to room temperature and then extracted with methylene chloride (3×75 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent removed in vacuo to yield a pure product (12.01 g; 100% yield). ^1H NMR (CDCl_3) δ 0.82–1.03 (m, 12H), 1.33–1.45 (m, 1H), 1.46–1.60 (m, 1H), 1.68–2.03 (m, 6H), 2.42–2.54 (m, 1H), 2.74–2.86 (m, 1H), 3.14–3.24 (t, 1H), 3.33–3.40 (d, 2H), 3.40–3.50 (m, 1H), 3.64–3.76 (s, 3H), 3.84–3.91 (d, 1H), 3.96–4.08 (m, 1H), 4.24–4.35 (m, 2H), 4.54–4.57 (d, 1H), 5.05–5.14 (d, 1H), 5.61–5.71 (d, 1H), 7.23–7.38 (m, 5H).

Synthesis of compound 5. A solution of 4 (12.01 g; 22.6 mmol) in dioxane (96 mL) was treated with a solution of potassium hydroxide (15.0 g; 240 mmol) in water (50 mL). The reaction mixture was stirred at room temperature overnight and then acidified with cold 10% HCl and the mixture extracted with ethyl acetate (3×250 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent removed to yield the product as a light-yellow hygroscopic foam (11.01 g; 94% yield).

Synthesis of compound 11. A solution of 5 (1.00 g; 2 mmol) in dry THF (5 mL) was added dropwise to a solution of 1,1'-carbonyl diimidazole (0.34 g; 2 mmol) in dry THF (5 mL). After the mixture was stirred for 0.5 h,

2-phenylethylamine (0.24 g; 2 mmol) was added and the solution stirred for 15 min. A solution of DBU (0.30 g; 2 mmol) in dry THF (8 mL) was added dropwise and the reaction mixture stirred for 2 h. The solvent was removed and the residue was dissolved in ethyl acetate (30 mL) and washed with 5% NaHCO_3 (10 mL), 5% HCl (10 mL), and brine (10 mL). The organic phase was dried and then evaporated to give a crude product which was purified using flash chromatography (silica gel/hexane/ethyl acetate gradient) to yield a white foam (0.75 g; 75% yield).

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