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## Route exploration and synthesis of the reported pyridone-based PDI inhibitor STK076545†

Eric Greve,<sup>a</sup> Sergey V. Lindeman,<sup>a</sup> Christina Scartelli,<sup>b</sup> Lin Lin,<sup>b</sup> Robert Flaumenhaft<sup>b</sup> and Chris Dockendorff<sup>✉</sup>

The enzyme protein disulfide isomerase (PDI) is essential for the correct folding of proteins and the activation of certain cell surface receptors, and is a promising target for the treatment of cancer and thrombotic conditions. A previous high-throughput screen identified the commercial compound STK076545 as a promising PDI inhibitor. To confirm its activity and support further biological studies, a resynthesis was pursued of the reported  $\beta$ -keto-amide with an *N*-alkylated pyridone at the  $\alpha$ -position. Numerous conventional approaches were complicated by undesired fragmentations or rearrangements. However, a successful 5-step synthetic route was achieved using an aldol reaction with an  $\alpha$ -pyridone allyl ester as a key step. An X-ray crystal structure of the final compound confirmed that the reported structure of STK076545 was achieved, however its lack of PDI activity and inconsistent spectral data suggest that the commercial structure was misassigned.

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## Introduction

Protein disulfide isomerase (PDI) is an enzyme primarily localized in the endoplasmic reticulum that catalyzes the oxidation–reduction and isomerization of disulfide bonds and serves as a necessary chaperone for protein folding.<sup>1</sup> In addition, PDI can be released onto the surface of endothelial and platelet cells, where it acts to promote effective coagulation *via* mechanisms presently under study. For these reasons, PDI inhibitors are of significant interest both for the treatment of cancer<sup>2</sup> and the prevention of thrombosis.<sup>3</sup> Several animal models of thrombosis have demonstrated that targeting cell surface PDI with antibodies or small molecules blocks both platelet accumulation and fibrin generation.<sup>4–8</sup> Previously reported PDI antagonists suffer from poor selectivity, irreversibility, and/or low potency. In an effort to identify novel inhibitors of PDI with more suitable therapeutic properties, a high-throughput screen was performed by Flaumenhaft and co-workers on approximately 5000 bioactive small molecules.<sup>6</sup> They identified a class of flavonoids called

quercertins, found in high abundance in various fruits and vegetables, that inhibit PDI. From this class, isoquercetin (Fig. 1) was found to decrease D-dimer plasma concentrations, a biomarker for venous thromboembolic disease, by a median of 22% in a phase II clinical trial.<sup>9</sup> However, the high dose and highly variable patients responses are drawbacks of isoquercetin.

To seek additional PDI inhibitors, a second high-throughput screen was performed on 348 505 compounds from the Molecular Libraries Small Molecule Repository.<sup>10</sup> Two series of PDI inhibitors, represented by bepristats **1a** and **2a** (Fig. 1) were found to bind to the hydrophobic pocket of the b'

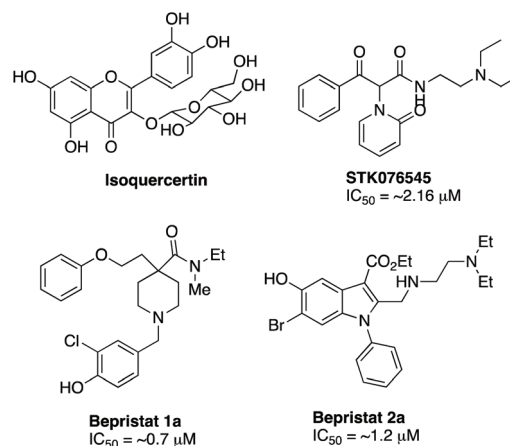


Fig. 1 Select inhibitors of PDI.

<sup>a</sup>Department of Chemistry, Marquette University, P.O. Box 1881, Milwaukee, WI, 53201-1881, USA. E-mail: christopher.dockendorff@mu.edu; Tel: +1-414-288-1617

<sup>b</sup>Division of Hemostasis and Thrombosis, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA

† Electronic supplementary information (ESI) available: <sup>1</sup>H and <sup>13</sup>C NMR spectra; additional X-ray crystallography figures and discussion. CCDC 2004020–2004023. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ob01205j

domain.<sup>8</sup> A commercial compound called STK076545 (Fig. 1) was also identified from the high-throughput screen to be a reasonably potent hit for the inhibition of PDI, and had an attractive structure for medicinal chemistry studies relative to other hits. The commercial supply of STK076545 was soon depleted, and we were unable to secure additional quantities, so we immediately endeavored to synthesize it. Its structure proved to be deceptively simple, and this manuscript describes several pitfalls that were encountered prior to its successful synthesis.

Methods for preparing  $\beta$ -keto amides have been pursued for more than a century.<sup>11</sup> The most obvious approach to  $\beta$ -keto amides is *via* amide couplings between  $\beta$ -keto acids and amines, which also permits late stage diversification for medicinal chemistry studies (Fig. 2, approach 'a'). However, this approach may be complicated by the limited stability of the  $\beta$ -keto acid starting materials, which can undergo decarboxylation (step 'b'). Alternatively, Meldrum's acid can be *C*-acylated, then aminolysis affords a  $\beta$ -keto amide, but this approach is limited to  $\alpha$ -unsubstituted substrates.<sup>12</sup> Direct aminolysis of  $\beta$ -keto esters<sup>13</sup> or  $\beta$ -keto thioesters<sup>14</sup> at high temperature is possible (approach 'c'), but can be compromised by competing enamine formation. Aminolysis reactions catalyzed with DMAP,<sup>15</sup> enzymes,<sup>16</sup> or transition metals<sup>17,18</sup> have also been reported. Alternatively, addition of a ketone or enamine to an isocyanate have also been reported (approach 'd'). Cross Claisen-like condensations of esters with amide enolates have been reported (approach 'e'),<sup>19,20</sup> or alternatively an aldol reaction between a pyridone-containing amide and a benzaldehyde (Ar = Ph for STK076545) could be envisaged, followed by alcohol oxidation (step 'f').

Other approaches involving a late stage addition of the pyridone are possible, but these were not initially considered since we were first interested in exploring amide structure-activity relationships (SARs), and the presence of a basic tertiary

amine on the amide side chain of STK076045 could complicate a late stage halogenation/pyridone *N*-alkylation reaction. It remained to be determined how the presence of an  $\alpha$ -pyridone could affect the steps outlined in Fig. 2. Herein, we report our explorations of these routes, culminating in a successful 5-step synthesis of the reported structure of STK076545. An initial version of this work was deposited in ChemRxiv on May 25<sup>th</sup>, 2020.<sup>21</sup>

## Results and discussion

### $\beta$ -Keto carboxylic acid

The initial synthetic route we envisioned to access STK076545 (Fig. 2, approach 'a') involved *N*-alkylation of 2-pyridone with bromo- $\beta$ -keto ester 2, followed by ester hydrolysis and amide coupling (Scheme 1). Using conditions previously reported using a bromomalonate,<sup>22</sup> both the *N*-alkylated 3 and *O*-alkylated 4 products were isolated, in 47% and 9% yield respectively. 3 and 4 were readily distinguishable based on their <sup>13</sup>C NMR chemical shifts for the  $\alpha$ -carbon, with the *O*-alkylated product 4 being assigned based on the more down-field  $\alpha$ -carbon peak at 75.9 ppm. In this paper, all alkylations of 2-pyridone gave *N*-alkylation as the major product, though the *O*-alkylated products were sometimes observed in trace amounts. Unfortunately, the hydrolysis of ester 3 under acidic (H<sub>2</sub>SO<sub>4</sub>) or basic conditions (NaOH, LiOH, or Me<sub>3</sub>SnOH<sup>23</sup>) all resulted in decarboxylation of carboxylic acid intermediate 6 to yield ketone 5, despite careful attempted isolations using buffered aqueous media. Direct coupling of alkali metal carboxylate salts has been shown by Batey and coworkers to be a useful strategy with unstable carboxylic acids.<sup>24</sup> Attempts at a tandem ester hydrolysis of 3 with NaOH or LiOH followed by peptide coupling with carboxylate 7 were not fruitful. Alternatively, the decarboxylation product 5 was synthesized on a larger scale *via* *N*-alkylation of 2-pyridone with 2-bromoacetophenone. Subsequent carboxylation using MgCl<sub>2</sub> and NaI with CO<sub>2</sub> also gave no detectable amount of carboxylate 8 or carboxylic acid 6 after an acidic workup.<sup>25</sup>

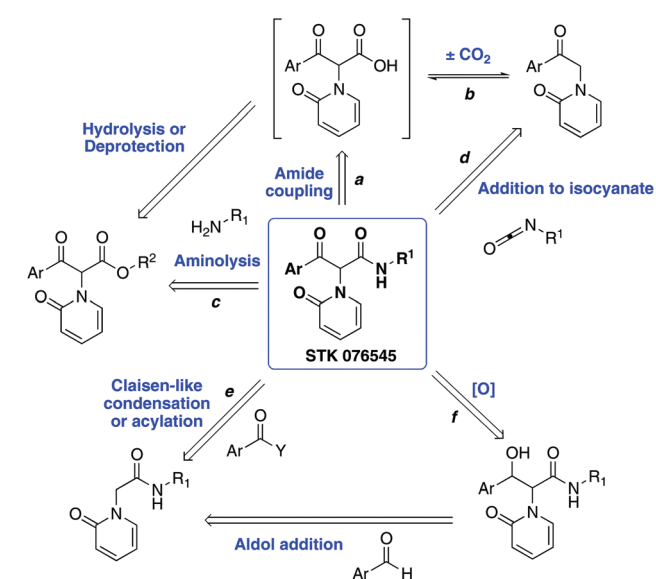
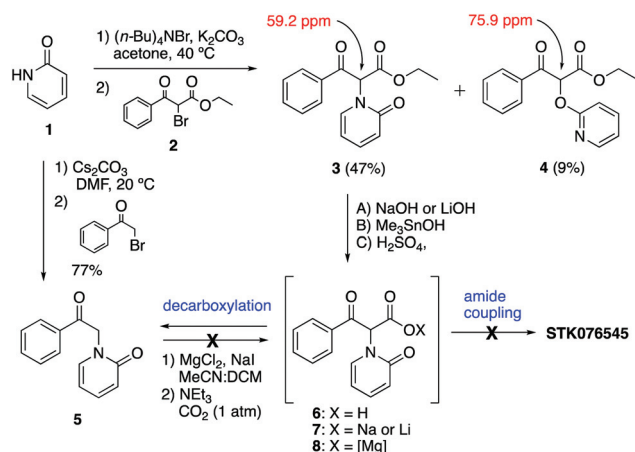
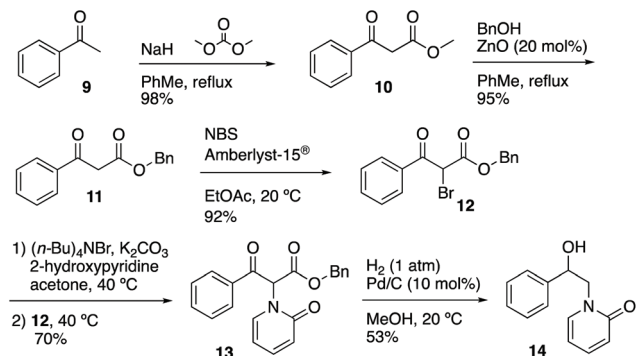


Fig. 2 Retrosynthetic strategies for accessing the  $\beta$ -keto amide in STK076545 (Ar = Ph, R<sup>1</sup> = -CH<sub>2</sub>CH<sub>2</sub>NEt<sub>2</sub>).



Scheme 1 Ester hydrolysis and carboxylate formation.



Scheme 2 Synthesis and deprotection of benzyl ester 13.

In an effort to access carboxylic acid 6 under milder conditions, the analogous benzyl ester intermediate 13 was synthesized in four steps (Scheme 2). First, 1,3-dicarbonyl 10 was prepared from acetophenone and dimethylcarbonate using NaH in 98% yield.<sup>26</sup> ZnO-catalyzed transesterification of 10 afforded benzyl alcohol 11.<sup>27</sup> Next, monohalogenation of 11 with NBS catalyzed by Amberlyst-15®, followed by reaction with 2-pyridone yielded  $\alpha$ -substituted- $\beta$ -keto ester 13 in 66% yield over two steps.<sup>28</sup> Benzyl removal from ester 13 *via* palladium-catalyzed hydrogenation also resulted in decarboxylation. In addition, <sup>1</sup>H NMR analysis of the crude product indicated the ketone was reduced to afford benzyl alcohol 14. Efforts to reduce the ketone prior to ester hydrolysis were not successful (Scheme 7).

### Enolate formation from ketone 5

Instead of proceeding through a carboxylic acid intermediate, we envisioned installation of the amide *via* reaction of an enolate with a suitable isocyanate, or reaction with CDI followed by addition of an amine to the intermediate acylimidazole (Fig. 2, approach 'd'). To identify suitable conditions for enolate formation with ketone 5, LDA, LiHMDS, and NaH were screened as bases (Table 1). Reactions were quenched at  $-78$  °C or  $20$  °C using D<sub>2</sub>O, and crude samples were analyzed

Table 1 Enolate formation from ketone 5

Entry	Base	Base (eq.)	T (°C) addition of base	T (°C) addition of D <sub>2</sub> O	% deuterium incorporation <sup>a</sup>
1 <sup>b</sup>	LDA	1.05	$-78$	$-78$	0
2 <sup>b</sup>	LiHMDS	1.05	$-78$	$-78$	0
3 <sup>b</sup>	LDA	1.05	$-78$	20	115
4 <sup>b</sup>	LiHMDS	1.05	$-78$	20	94
5 <sup>c</sup>	NaH	1.2	20	20	134

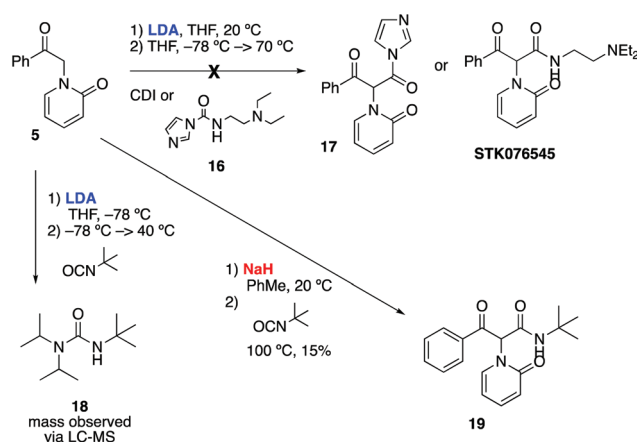
<sup>a</sup> Deuterium incorporation was determined *via* <sup>1</sup>H NMR. <sup>b</sup> 12.5 mg of 5 was used in this reaction. <sup>c</sup> 25 mg of 5 was used in this reaction.

*via* <sup>1</sup>H NMR. Based on our screen, it was found that all reactions occurring at  $20$  °C facilitated enolate formation (entries 3–5), while no deuterium incorporation occurred when quenching the samples at  $-78$  °C (entries 1 and 2). The observed deuterium incorporation over 100% is expected to be within the systematic error associated with the preparation of LDA or the weight of NaH, and <sup>1</sup>H NMR integrations of these small scale reactions.

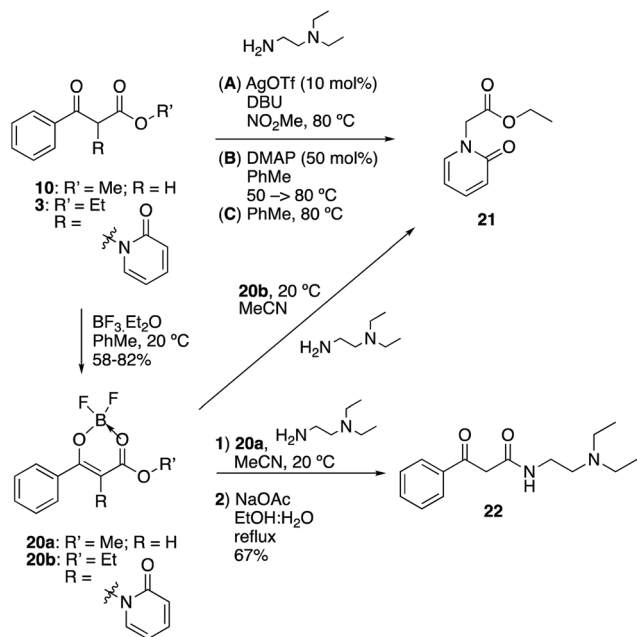
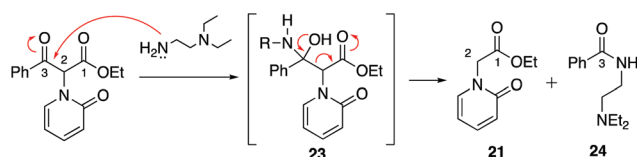
The enolate from ketone 5 was next formed using LDA at  $20$  °C and reacted with CDI or urea intermediate 16, synthesized from CDI and *N,N*-diethylethylenediamine (Scheme 3). There was no observable reaction with either electrophile, even after heating at  $70$  °C. We then tested commercially available *tert*-butyl isocyanate as a model isocyanate for reaction screening. When LDA was used as a base, no desired product was observed. Rather, urea byproduct 18 formed from the addition of diisopropylamine to *tert*-butyl isocyanate was detected *via* LC-MS. Switching to NaH as the base and heating the reaction at  $100$  °C for 2 h in toluene yielded amide 19 in 15% yield. Efforts to synthesize the desired isocyanate from *N,N*-diethylethylenediamine and triphosgene, or reacting diethylamine with 2-bromoethyl isocyanate, were both troublesome. With this synthetic route being low yielding and having the limitation of only producing secondary amides, we chose to seek an alternative route.

### Direct aminolysis of $\beta$ -keto ester

Another common synthetic approach to access amides is *via* direct aminolysis of esters (Fig. 2, approach 'c'). Starting from  $\beta$ -keto ester 3, we first tested a Ag(I)-catalyzed aminolysis (Scheme 4).<sup>18</sup> Rather than observing conversion to the desired  $\beta$ -keto amide, reaction monitoring *via* LC-MS when using condition A showed masses associated with ester 21 and amide 24 (Scheme 5). Similarly, when heating ester 3 with *N,N*-diethylethylenediamine in toluene at  $80$  °C with or without DMAP, the same decomposition peaks were present. Ester 21 was isolated when using conditions B and correlated with the mass peak observed *via* LC-MS. Ag(I)/DBU and DMAP were found to



Scheme 3 Enolate reactions with ketone 5.

Scheme 4 Direct aminolysis attempts with  $\beta$ -keto esters.

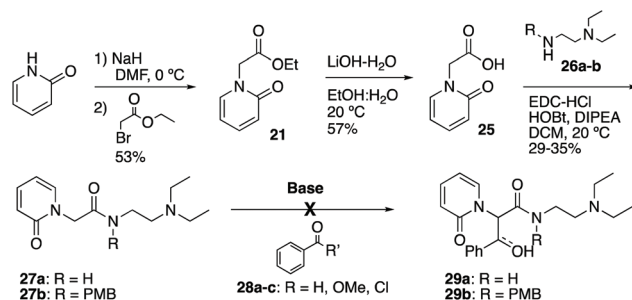
Scheme 5 Proposed retro Claisen-like condensation decomposition.

both accelerate the conversion to **21** in a few hours, in comparison to the reaction heated in toluene that proceeded slowly over 24 h. We hypothesize that the  $\beta$ -keto ester decomposes *via* a retro Claisen-like condensation mechanism. The amine (or nucleophilic catalyst) could add to the ketone, followed by collapse of the tetrahedral intermediate **23** and cleavage of the C–C bond to produce ester **21** (Scheme 5).

Stefane and Polanc reported a method to prepare  $\beta$ -keto amides from  $\beta$ -keto esters that proceeds *via* a 1,3,2-dioxaborinane intermediate.<sup>29</sup> Reacting  $\beta$ -keto ester **3** with boron trifluoride etherate afforded the boron complex **20b** in 82% yield (Scheme 4). Unfortunately, subsequent treatment of **20b** with *N,N*-diethylethylenediamine also resulted in decomposition to ester **21** after only 1 h, and complete decomposition after 24 h. Interestingly, when starting from  $\beta$ -keto ester **10** which does not have the pyridone substituent in the  $\alpha$  position, the preparation of the boron complex **20a** and treatment with *N,N*-diethylethylenediamine cleanly afforded  $\beta$ -keto amide **22**.

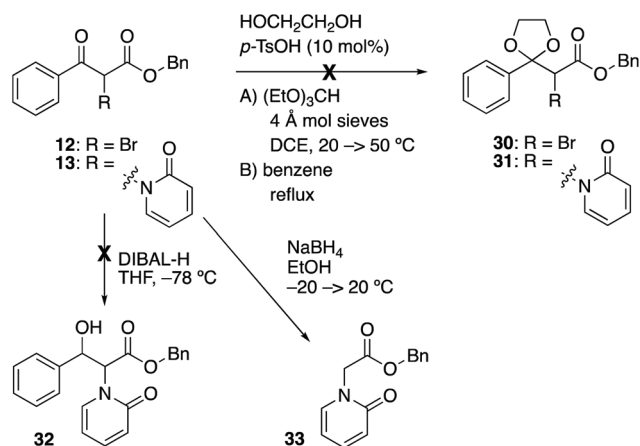
### Late stage C2–C3 coupling route

Inspired by our observed retro Claisen-like reaction that occurred with a  $\beta$ -keto ester substrate, we examined the feasibility of performing an aldol addition, Claisen-like condensation, or acylation with intermediates **27a–b** (Scheme 6). Thus,

Scheme 6 C2–C3 coupling attempts on amide **26a–b**.

installation of the C2–C3 bond would occur after amide formation and minimize the possibility of decarboxylation. Synthesis of **27a–b** began with *N*-alkylation of 2-pyridone with ethyl bromoacetate followed by ester hydrolysis, affording the previously reported carboxylic acid **25**.<sup>30</sup> Amide coupling with either *N,N*-diethylethylenediamine **26a** or PMB-protected amine **26b** yielded amides **27a–b**. We prepared the PMB-protected amide **26b** in an effort to avoid competitive deprotonation of the amide proton during enolization reactions. Extensive efforts to react these pronucleophiles with different bases (NaOMe, NaH, and LDA), electrophiles (aldehyde, ester, or acid chlorides **28a–c**), and at variable temperatures (0–160 °C) were all unfruitful.

Identification of the aldol adduct as a possible intermediate provided inspiration to access alcohol **32**, which would not undergo decarboxylation during ester hydrolysis (Scheme 7). Starting from benzyl esters **12** or **13**, we attempted to either protect or reduce the benzylic ketone. Efforts to protect the ketone using ethylene glycol and catalytic *p*-TsOH with triethyl orthoformate and 4 Å mol sieves or a Dean–Stark trap resulted in no conversion. Alternatively, an attempt to reduce the ketone with DIBAL-H resulted in pyridone reduction, as suggested by the crude <sup>1</sup>H NMR spectrum. Switching to NaBH<sub>4</sub>

Scheme 7 Attempted protection and reduction reactions of benzylic ketone **12** and **13**.





X-ray structure of **42b** is the relative stereochemistry between the hydroxyl and pyridone substituents. We propose that cyclic acetoxonium ion intermediate **43** is formed, similar to that proposed for the Prévost<sup>33</sup> and Woodward<sup>34</sup> dihydroxylation reactions, and 2-pyridone then attacks the benzylic carbon. Since we started with (*E*)-methyl cinnamate, the *anti* addition of water to the intermediate *rac*-bromonium ion results in a racemic mixture of bromohydrins **39**. Formation of the proposed acetoxonium ion intermediate **43** and subsequent pyridone alkylation would result in inversion of both stereocenters and generate **40b**. Ester hydrolysis of **40b** then yielded acid **42b**, with its relative stereochemistry confirmed by the X-ray crystal structure (Scheme 9).

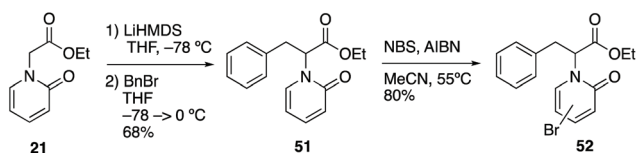
### Aldol addition route

To circumvent the unexpected rearrangement through the acetoxonium ion intermediate, we planned to perform the *N*-alkylation prior to installation of the alcohol/ketone functionality. Inspired by Easton and co-workers' use of NBS and AgNO<sub>3</sub> to generate hydroxy- $\alpha$ -amino acid derivatives,<sup>35</sup> we sought to access a benzylic bromide intermediate from **51** (Scheme 11). Ester **21** was reacted with LiHMDS to generate an enolate, followed by alkylation with benzyl bromide to afford **51**. Subsequent treatment with NBS and AIBN in MeCN yielded no bromination at the benzylic position. The *m/z* peak observed in the LC-MS trace confirmed the presence of a brominated product, but the crude <sup>1</sup>H NMR spectrum suggested that bromination occurred on the pyridone. Alternatively, benzaldehyde was used instead of benzyl bromide to react with the enolate generated from ester **21** to access the benzylic

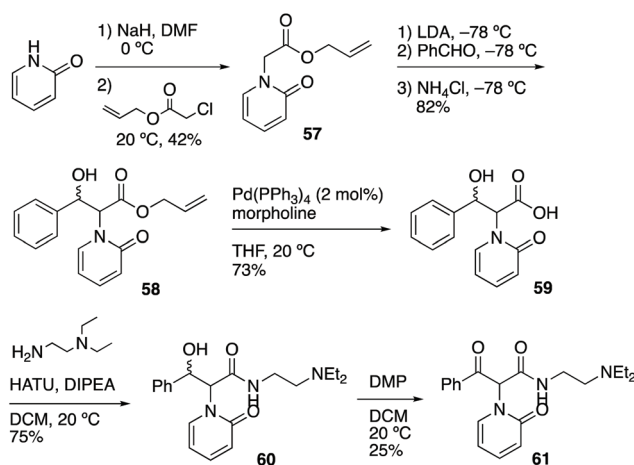
alcohol directly (Scheme 12). Using identical conditions (LiHMDS and 0 °C), the elimination product **53** was generated. Hydrolysis of ester **53** yielded carboxylic acid **54**, which X-ray crystallography confirmed to be the *Z* alkene.

With LDA being more commonly used in the literature for aldol addition reactions with esters, we switched our base to LDA (Scheme 12). Quenching the reaction at -78 °C was found to be critical to avoid generation of the elimination product and give the desired alcohol **55**. Unfortunately, ester hydrolysis with LiOH yielded the elimination product **53** again. In an effort to avoid generation of this undesired alkene, we synthesized the TBS-protected alcohol **56**. This route was unfruitful as ester hydrolysis or cleavage using LiOH, Me<sub>3</sub>SnOH, or LiI all resulted in the generation of **53**.

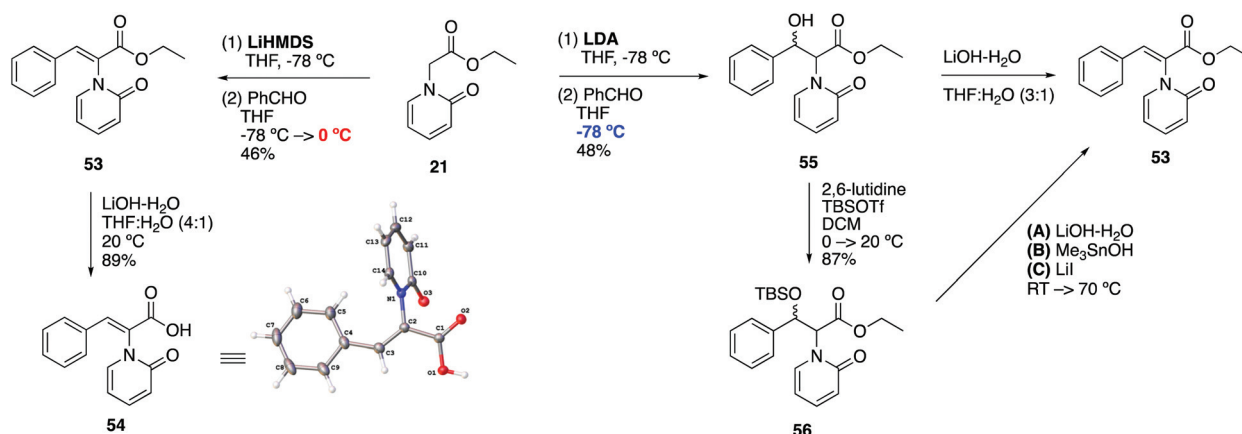
In order to access the carboxylic acid under milder conditions, we instead synthesized allyl ester **57** (Scheme 13). First, 2-pyridone was alkylated with allyl chloroacetate to yield allyl ester **57**, and subsequent aldol addition using benzaldehyde afforded alcohol **58**. By increasing the amount of benzaldehyde from 1 to 2 equivalents, we were able to nearly



Scheme 11 Alkylation and attempted benzylic bromination.



Scheme 13 Successful allyl ester route to STK076545.



Scheme 12 Aldol reactions with  $\alpha$ -pyridone ester **21**.

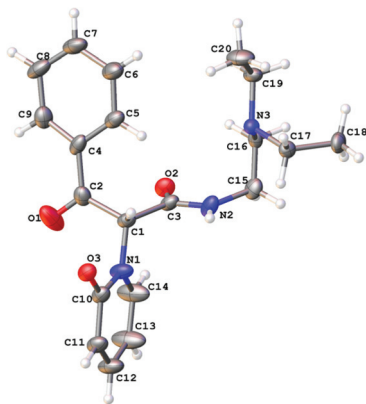


Fig. 3 X-ray structure of amide **61**.

double the yield to 82% for this reaction. Allyl removal with Pd(PPh<sub>3</sub>)<sub>4</sub> produced carboxylic acid **59**. Amide coupling and subsequent DMP oxidation of alcohol **60** successfully produced the final  $\beta$ -keto-amide product **61** with the reported structure of STK076545. Incomplete conversion and uncharacterized byproducts were observed with the low yielding DMP oxidation. Alternative oxidation conditions (*e.g.* PDC, MnO<sub>2</sub>, Bobbitt's salt,<sup>32</sup> and Cu catalyzed aerobic oxidation<sup>36</sup>) were all unsuccessful. We obtained an X-ray crystal structure corroborating the structure of **61** (Fig. 3). Alcohol analog **60**, the final compound **61**, and its regioisomeric analog **50** were tested in an assay measuring PDI-catalyzed insulin reduction and aggregation. All compounds were found to be inactive, with rutin used as a positive control (Fig. 4, see Experimental section for details). Interestingly, the <sup>1</sup>H NMR spectrum of **61** does not match that of the STK076545 received from the commercial

supplier (Table 2). This confirms that the structure of the active PDI-inhibiting compound was misassigned.

## Conclusion

Several conventional methods for forming  $\beta$ -keto amides resulted in fragmentation of pyridone-containing intermediates, such as retro-Claisen-like and retro-aldol reactions. Efforts to instead proceed *via* an acetyl protected bromohydrin resulted in a rearrangement that we propose proceeds *via* an acetoxonium ion intermediate. Alternatively, we successfully synthesized the reported structure of STK076545 in 5% overall yield (unoptimized) *via* a 5-step synthetic route proceeding through allyl ester **58**. This strategy should prove to be broadly useful in accessing  $\beta$ -keto amides, particularly with an electron-withdrawing  $\alpha$ -substituent such as *N*-pyridone. Unexpectedly, neither the final compound (**61**) nor several of its analogs were found to inhibit protein disulfide isomerase, and its <sup>1</sup>H NMR spectrum does not match that of the active commercial compound STK076545. It is not uncommon for complex natural products to have misassigned structures which require correction after more detailed synthetic and spectroscopic studies.<sup>37</sup> However, it is often taken for granted that simpler commercial small molecules are provided in high purity and with structures as advertised, which is not always the case.<sup>38</sup> Our results here highlight the importance of resynthesis and structure validation of active compounds prior to embarking on medicinal chemistry campaigns. Current efforts in our lab are ongoing to elucidate the correct structure of the commercially supplied compound that may have useful PDI inhibitory activity.

## Experimental section

### General information

All reagents and solvents were purchased from commercial vendors and used as received, except for diethylamine, which was distilled and stored over 4 Å mol sieves prior to use. Deionized water was purified by charcoal filtration and used for reaction workups and in reactions with water. NMR spectra were recorded on Varian 300 MHz or 400 MHz spectrometers as indicated. Proton and carbon chemical shifts are reported in parts per million (ppm;  $\delta$ ) relative to tetramethylsilane, CDCl<sub>3</sub>, or CD<sub>3</sub>OD (<sup>1</sup>H  $\delta$  0, <sup>13</sup>C  $\delta$  77.16, or <sup>1</sup>H  $\delta$  3.31, <sup>13</sup>C  $\delta$  49.0, respectively). NMR data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet); coupling constant(s) in Hz; integration. Unless otherwise indicated, NMR data were collected at 25 °C. NMR data were processed using MestReNova software. Flash chromatography was performed using Biotage SNAP cartridges filled with 40–60  $\mu$ m silica gel, or C18 reverse phase columns (Biotage® SNAP Ultra 18) on Biotage Isolera systems, with photodiode array UV detectors. Analytical thin layer chromatography (TLC) was performed on Agela

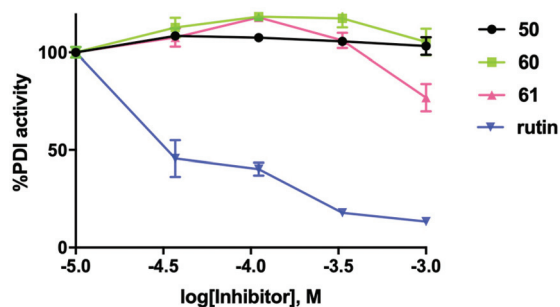


Fig. 4 PDI-mediated insulin aggregation assay.

Table 2 <sup>1</sup>H NMR chemical shifts of STK076545 and **61**

Entry	Compound	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) $\delta$ (integration)
1	STK076545	8.83 (1H), 8.05 (2H), 7.46 (1H), 7.39 (2H), 7.31 (1H), 7.25 (1H), 6.55 (1H), 6.15 (1H), 4.57 (2H), 3.57 (2H), 2.93 (6H), 2.62 (1H), 1.21 (6H)
2	<b>61</b>	8.01 (2H), 7.65 (1H), 7.60–7.56 (1H), 7.48–7.44 (1H), 7.40–7.34 (2H), 6.60 (1H), 6.24 (1H), 3.39–3.28 (2H), 2.57–2.48 (6H), 0.96 (6H)

Technologies glass plates with 0.25 mm silica gel with F254 indicator. Visualization was accomplished with UV light (254 nm) and aqueous potassium permanganate (KMnO<sub>4</sub>) stain followed by heating, unless otherwise noted. Tandem liquid chromatography/mass spectrometry (LC-MS) was performed on a Shimadzu LCMS-2020 with autosampler, photodiode array detector, and single-quadrupole MS with ESI and APCI dual ionization, using a Peak Scientific nitrogen generator. Unless otherwise noted, a standard LC-MS method was used to analyze reactions and reaction products: Phenomenex Gemini C18 column (100 × 4.6 mm, 3 μm particle size, 110 Å pore size); column temperature 40 °C; 5 μL of sample in MeOH or CH<sub>3</sub>CN at a nominal concentration of 1 mg mL<sup>-1</sup> was injected, and peaks were eluted with a gradient of 25–95% CH<sub>3</sub>CN/H<sub>2</sub>O (both with 0.1% formic acid) over 5 min, then 95% CH<sub>3</sub>CN/H<sub>2</sub>O for 2 min.

### Synthetic protocols

**Ethyl 3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (3); ethyl 3-oxo-3-phenyl-2-(pyridin-2-yloxy)propanoate (4).** A suspension of 2-hydroxypyridone (163 mg, 1.72 mmol), tetrabutylammonium bromide (59.5 mg, 0.184 mmol), and potassium carbonate (765 mg, 55.3 mmol) in acetone (6.0 mL) was heated to 40 °C and stirred for 30 min. Ethyl-2-bromo-3-oxo-3-phenylpropanoate (500 mg, 1.84 mmol) was added and the suspension was stirred at 40 °C for 30 min before being cooled to 20 °C. A solution of acetic acid (160 μL, 2.79 mmol) in water (2.0 mL) was added slowly, and the mixture was stirred for 15 min. The resulting mixture was diluted with H<sub>2</sub>O (2.0 mL) and extracted with DCM (3 × 15 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude orange oil was dissolved in DCM and purified *via* flash chromatography (25 g SiO<sub>2</sub> column, 0–60% EtOAc/hexanes) to yield pyridone **3** as a yellow oil (229 mg, 47%) and **4** as a yellow oil (44 mg, 9%). **3**: *R*<sub>f</sub> = 0.25 (50 : 50 EtOAc : hexanes); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.09 (d, *J* = 7.3 Hz, 2H), 7.64–7.58 (m, 2H), 7.51–7.46 (m, 3H), 7.37–7.33 (m, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 6.22–6.18 (m, 1H), 4.31–4.28 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 191.9, 166.6, 161.4, 140.6, 136.4, 134.8, 134.0, 129.4, 129.2, 120.2, 106.4, 62.8, 59.2, 14.1; LC-MS *t*<sub>R</sub> = 3.96; *m/z* = 285.75 (*M* + *H*); **4**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.11–8.05 (m, 3H), 7.63–7.58 (m, 2H), 7.51–7.46 (m, 2H), 6.98–6.92 (m, 2H), 6.68 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 191.7, 166.6, 161.3, 146.5, 139.3, 133.9, 129.4, 128.7, 118.3, 111.4, 76.0, 62.2, 14.1; LC-MS *t*<sub>R</sub> = 2.86; *m/z* = 285.75 (*M* + *H*).

**1-(2-Oxo-2-phenylethyl)-1,2-dihydropyridin-2-one (5).** 2-Hydroxypyridine (0.263 g, 2.76 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.63 g, 5.02 mmol) were added to a 15 mL oven-dried flask with stir bar and sealed under N<sub>2</sub>. Anhydrous DMF (5.0 mL) was added and the suspension was stirred at 20 °C for 30 min before 2-bromoacetophenone (0.500 g, 2.51 mmol) was added and the suspension was stirred for an additional 1 h at 20 °C. A solution of glacial acetic acid (210 μL, 3.77 mmol) in H<sub>2</sub>O (2 mL) was slowly added and the mixture was stirred until it

turned clear and stopped bubbling (~10 min). The mixture was diluted with H<sub>2</sub>O (5 mL) and EtOAc (40 mL) and the layers were separated. The organic layer was washed with water (3 × 15 mL) and the combined aqueous layers were extracted with EtOAc (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude yellow solid was dissolved in DCM and purified *via* flash chromatography (50 g SiO<sub>2</sub> column, 0–100% EtOAc/hexanes) to yield pyridone **5** as a white crystalline solid (0.411 g, 77%). This compound has been previously reported and characterized (CAS# 952-75-0). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.02–8.00 (m, 2H), 7.62 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.51–7.47 (m, 1H), 7.40–7.35 (m, 1H), 7.23–7.21 (m, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 6.21 (td, *J* = 6.7, 1.3 Hz, 1H), 2.21 (s, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 192.4, 162.5, 140.2, 138.4, 134.7, 134.1, 129.0, 128.2, 120.8, 106.1, 54.4.

**Methyl 3-oxo-3-phenylpropanoate (10).** NaH (3.7 g, 60% in mineral oil, 92 mmol) and dimethyl carbonate (5.9 g, 66 mmol) were added to a 250 mL oven-dried flask with stir bar. A reflux condenser and addition funnel were attached, the apparatus was sealed and flushed with N<sub>2</sub>, and anhydrous toluene (33 mL) was added under N<sub>2</sub>. After the mixture was heated to reflux, a solution of acetophenone (3.80 mL, 32.4 mmol) in toluene (17 mL) was added dropwise over 0.5 h. The reaction solution turned orange with the formation of a white precipitate. After the evolution of hydrogen ceased (~15 min), the reaction was cooled to room temperature. Glacial acetic acid (10 mL) was added dropwise and a heavy pasty solid separated. Ice-cold water was slowly added until the solid dissolved completely, and the reaction mixture was diluted with EtOAc (200 mL). The organic layer was separated, washed with H<sub>2</sub>O (200 mL) and brine (200 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was dissolved in DCM and purified *via* flash chromatography (100 g SiO<sub>2</sub> column, 0–25% EtOAc/hexanes) to yield ester **10** as an orange oil (5.65 g, 98%). This compound has been previously reported and characterized (CAS# 614-27-7).<sup>26</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 12.51 (s, 0.22 H), 7.94 (m, 2H), 7.78 (m, 0.44 H), 7.76–7.58 (m, 0.44 H), 7.62–7.58 (m, 1 H), 7.50–7.40 (m, 2.7 H), 5.68 (s, 0.22 H), 4.01 (s, 2H), 3.80 (s, 0.65 H), 3.75 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 192.5, 173.6, 171.6, 168.0, 136.0, 133.9, 133.4, 131.4, 128.9, 128.64, 128.6, 126.2, 87.1, 52.6, 51.5, 45.8.

**Benzyl 3-oxo-3-phenylpropanoate (11).** A 25 mL round bottom flask was charged with methyl 3-oxo-3-phenylpropanoate (1.05 g, 5.91 mmol), benzyl alcohol (6.10 mL, 59.1 mmol), ZnO (96.0 mg, 1.18 mmol) and anhydrous toluene (5 mL). The flask was fitted with a short-path distillation head and heated in an oil bath set at 110 °C, distilling the methanol formed during the reaction. After 24 h, LC-MS analysis of the reaction mixture showed complete consumption of the starting material. The reaction mixture was filtered through a plug of celite and concentrated. The crude residue was dissolved in DCM and purified *via* flash chromatography (100 g SiO<sub>2</sub> column, 0–20% EtOAc/hexanes) to give benzyl ester **11** as a light orange oil (1.43 g, 95%). This compound has been pre-



viously reported and characterized (CAS# 63888-22-2).<sup>39</sup> This compound exists as a mixture of tautomers in CDCl<sub>3</sub> (10 : 1 keto : enol). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 12.50 (s, enol), 7.94 (d, *J* = 8.0 Hz, enol), 7.90 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 7.9 Hz, enol), 7.59 (t, *J* = 7.5 Hz, 1H), 7.48–7.28 (m, 7H), 5.73 (s, enol), 5.25 (s, enol), 5.19 (s, 2H), 4.04 (s, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 192.4, 167.5, 135.4, 133.9, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 67.3, 46.1.

**Benzyl 2-bromo-3-oxo-3-phenylpropanoate (12).** In a 100 mL flask with stir bar, ester **11** (1.00 g, 3.93 mmol), *N*-bromosuccinimide (0.735 g, 4.13 mmol), and Amberlyst-15 (2.89 g) in ethyl acetate (30 mL) were stirred at 20 °C for 2.5 h. After completion of the reaction, as indicated by LC-MS, the reaction mixture was filtered and washed with EtOAc (2 × 20 mL). The combined organic filtrates were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The crude product was dissolved in DCM and purified *via* flash chromatography (50 g SiO<sub>2</sub> column, 0–20% EtOAc/hexanes) to yield alkyl bromide **12** as a light yellow oil (1.20 g, 92%). This compound has been previously reported and characterized (CAS# 845733-96-2).<sup>28</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.94–7.92 (m, 2H), 7.58 (m, 1H), 7.43 (m, 2H), 7.30–7.23 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 188.0, 165.1, 134.6, 134.3, 133.3, 129.2, 128.9, 128.6, 128.6, 128.4, 68.8, 46.4.

**Benzyl 3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (13).** A suspension of 2-hydroxypyridone (212 mg, 2.23 mmol), tetrabutylammonium bromide (65.4 mg, 0.203 mmol), and potassium carbonate (0.841 g, 6.09 mmol) in acetone (4.0 mL) was heated to 40 °C and stirred for 30 min. Then, bromide **12** (676 mg, 2.03 mmol) in acetone (0.5 mL) was added. The suspension was stirred at 40 °C for 30 min and cooled to room temperature before a solution of acetic acid (232 μL, 4.06 mmol) in water (2.0 mL) was added slowly. The resulting mixture was stirred for 15 min before it was diluted with H<sub>2</sub>O (5.0 mL) and extracted with DCM (3 × 15 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude dark orange oil was dissolved in DCM and purified *via* flash chromatography (50 g SiO<sub>2</sub>, 0–50% EtOAc/hexanes) to yield pyridone **13** as a colorless oil (496 mg, 70%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.07–8.04 (m, 2H), 7.64 (s, 1H), 7.60 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.48–7.44 (m, 3H), 7.35–7.26 (m, 6H), 6.61 (d, *J* = 9.2 Hz, 1H), 6.18 (td, *J* = 6.8 Hz, 1.3 Hz, 1H), 5.25 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 191.7, 166.5, 161.4, 140.7, 136.4, 134.8, 134.6, 133.9, 129.4, 129.2, 128.7, 128.7, 128.4, 120.3, 106.4, 68.3, 59.4; LC-MS *t*<sub>R</sub> = 3.72; *m/z* = 348.10 (M + H).

**1-(2-Hydroxy-2-phenylethyl)-1,2-dihydropyridin-2-one (14).** To a 15 mL flask with stir bar, **13** (33.5 mg, 0.096 mmol) and MeOH (3.0 mL) were added. The flask headspace was flushed with N<sub>2</sub> before 10% Pd/C (10.3, 0.0096 mmol) was added. The flask was flushed with H<sub>2</sub> and stirred under H<sub>2</sub> (1 atm) at 20 °C for 1 h. After 1 h, the reaction mixture was filtered through celite, condensed under vacuum and analyzed *via* LC-MS and <sup>1</sup>H NMR, which indicated conversion to alcohol **14**. <sup>1</sup>H NMR of the crude product showed signals for alkyl protons at 4.36, 3.89, and 5.01 ppm, consistent with published data.

This compound has been previously reported and characterized (CAS# 69914-21-2).<sup>40</sup> <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.43–7.39 (m, 2H), 7.39–7.33 (m, 3H), 7.29–7.26 (m, 2H), 6.56 (d, *J* = 8.5 Hz, 1H), 6.30 (td, *J* = 6.7, 1.2 Hz, 1H), 5.01 (dd, *J* = 8.8, 3.8 Hz, 1H), 4.36 (dd, *J* = 13.1, 3.8 Hz, 1H), 3.89 (dd, *J* = 13.1, 8.8 Hz, 1H). 215.75; LC-MS *t*<sub>R</sub> = 1.68; *m/z* = 215.75 (M + H).

***N*-[2-(Diethylamino)ethyl]-1*H*-imidazole-1-carboxamide (16).** 1,1-Carbonyldiimidazole (205 mg, 1.26 mmol) was added to a 4 mL oven-dried vial with stir bar and sealed under N<sub>2</sub>. Anhydrous THF (1.2 mL) was added and the solution was cooled to 0 °C in an ice bath. A solution of *N,N*-diethylethylenediamine (97.9 mg, 0.842 mmol) in anhydrous DCM (0.6 mL) was added dropwise over 10 min and the solution was stirred at 20 °C for 1.5 h. Next, the solvent was removed *via* vacuum and the crude product was loaded on to celite and purified *via* flash chromatography (12 g C18, MeOH/H<sub>2</sub>O gradient) to yield urea **16** as a yellow oil (93.7 mg, 53%). This compound has been previously reported (CAS# 698388-51-1).<sup>41</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.18 (s, 1H), 7.45–7.42 (m, 1H), 7.09–7.07 (m, 2H), 3.46 (t, *J* = 6.1 Hz, 2H), 2.66 (t, *J* = 5.6 Hz, 2H), 2.61–2.51 (m, 4H), 1.06–0.97 (m, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 149.1, 136.1, 130.3, 130.1, 116.1, 51.3, 46.8, 38.2, 11.8; LC-MS *t*<sub>R</sub> = 1.01; *m/z* = 210.80 (M + H).

***N*-tert-Butyl-3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (19).** In a 4 mL oven-dried vial with a stir bar, *t*-butylisocyanate (7.0 mg, 0.071 mmol) and NaH (60% w/w in mineral oil, 4.7 mg, 0.118 mmol) were mixed in anhydrous toluene (0.5 mL) under N<sub>2</sub> at 20 °C. Then, ketone **5** (10.0 mg, 0.047 mmol) was added in one portion and the mixture was heated at 100 °C for 2 h. After 2 h, the reaction was quenched by the addition of saturated ammonium chloride. The aqueous layer was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and condensed to a yellow residue. The crude product was purified *via* flash chromatography (10 g SiO<sub>2</sub>, 0–100% EtOAc/hexanes) to afford amide **19** as a yellow oil (2.2 mg, 15%) and recovered ketone **5** (8.0 mg, 80%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.74–7.72 (m, 1H), 7.56–7.52 (m, 1H), 7.43–7.36 (m, 3H), 7.31 (s, 1H), 6.85 (br s, 1H), 6.61 (d, *J* = 9.0 Hz, 1H), 6.29 (t, *J* = 6.8 Hz, 1H). LC-MS *t*<sub>R</sub> = 2.96; *m/z* = 313.15 (M + H).

**2,2-Difluoro-6-methoxy-4-phenyl-2*H*-1λ<sup>3</sup>,3,2λ<sup>4</sup>-dioxaborinine (20a).** To an oven-dried 20 mL vial, **10** (0.420 g, 2.36 mmol) and a stir bar were added and the vial was purged with N<sub>2</sub> for 10 min. Then, anhydrous toluene (10 mL) and boron trifluoride etherate (0.58 mL, 4.71 mmol) were sequentially added. The reaction mixture was stirred at 20 °C for 20 h. The reaction mixture was then concentrated to ~1/3 of its volume and cooled to –30 °C in a dry ice MeOH/H<sub>2</sub>O cooling bath. The precipitated material was filtered off and washed with 5 : 1 petroleum ether/EtOAc (5 mL), yielding the boron complex **20a** as a yellow solid (307 mg, 58%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.96–7.92 (m, 2H), 7.63–7.57 (m, 1H), 7.51–7.46 (2H), 6.03 (s, 1H), 4.12 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 179.6, 176.3, 134.0, 132.0, 129.0, 127.9, 83.2, 56.1.

**Ethyl 2-(2-oxo-1,2-dihydropyridin-1-yl)acetate (21).** To an oven-dried 1.0 L round bottom flask charged with a stir bar, NaH (60% in mineral oil, 1.99 g, 49.9 mmol) was suspended in anhydrous DMF (100 mL) and cooled to 0 °C in an ice bath under N<sub>2</sub>. To the NaH suspension, a solution of 2-hydroxypyridine (4.07 g, 42.1 mmol) in anhydrous DMF (200 mL) was slowly added. The resulting solution was stirred for 1 h at 0 °C before ethyl bromoacetate (4.3 mL, 38 mmol) was added and the mixture was stirred at room temperature for 1.5 h. The reaction was quenched with saturated NH<sub>4</sub>Cl (40 mL) and the product was extracted with DCM (3 × 150 mL). The combined organic extracts were washed with water (7 × 200 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was dissolved in DCM and purified *via* flash chromatography (100 g SiO<sub>2</sub>, 0–100% EtOAc/hexanes) to yield ester **21** as a pale yellow oil (3.62 g, 53%). This compound has been previously reported and characterized (CAS# 80056-43-5).<sup>30</sup> *R*<sub>f</sub> = 0.74 (DCM/MeOH 9 : 1). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.29 (t, 3H, *J* = 7.1 Hz), 4.24 (q, 2H, *J* = 7.1 Hz), 4.64 (s, 2H), 6.18–6.23 (m, 1H), 6.58–6.61 (m, 1H), 7.21–7.24 (m, 1H), 7.34–7.40 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.2, 50.5, 61.9, 106.2, 121.0, 121.0, 138.0, 140.3, 162.5, 167.9.

***N*-[2-(Diethylamino)ethyl]-3-oxo-3-phenylpropanamide (22).** *N,N*-Diethylethylenediamine (167.0 mg, 1.438 mmol) was added to a 15 mL oven-dried flask with stir bar and sealed under N<sub>2</sub>. Anhydrous MeCN (5.0 mL) and **20a** (250 mg, 1.11 mmol) were added, and the reaction mixture was stirred at 20 °C for 4 h. After 4 h, an aliquot was removed, condensed under reduced pressure, and dissolved in CDCl<sub>3</sub> to monitor the reaction *via* <sup>1</sup>H NMR. The reaction mixture was condensed under vacuum, dissolved in EtOAc (30 mL), washed with H<sub>2</sub>O (2 × 10 mL), dried over MgSO<sub>4</sub>, filtered, and condensed under vacuum to yield complex **22** as a pale yellow oil (283 mg, 82%). The crude oil (259 mg, 0.834 mmol), sodium acetate (0.342 g, 4.17 mmol), ethanol (5.0 mL), and H<sub>2</sub>O (5.0 mL) were refluxed for 8 h. TLC analysis (10% MeOH/DCM) of the reaction mixture indicated the starting material was consumed. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (30 mL) and washed with water (2 × 10 mL). The combined aqueous layers were saturated with NaCl and extracted with 9 : 1 DCM : MeOH (5 × 10 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated. The crude oil was purified by flash chromatography (10 g SiO<sub>2</sub>, 0–10% MeOH/DCM) to yield amide **22** as a pale yellow oil (147 mg, 67%). *R*<sub>f</sub> = 0.50 (9 : 1 DCM : MeOH); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.99 (d, *J* = 7.4 Hz, 2H), 7.61–7.57 (m, 1H), 7.50–7.45 (m, 2H), 3.96 (s, 2H), 3.48 (q, *J* = 5.5 Hz, 2H), 2.79–2.73 (m, 6H), 1.14 (t, *J* = 7.1 Hz, 6H); <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>) δ 195.16, 178.19, 136.43, 133.82, 128.84, 128.70, 51.54, 47.03, 46.53, 36.49, 10.50; LC-MS *t*<sub>R</sub> = 1.06; *m/z* = 263.15 (M + H).

**2-(2-Oxo-1,2-dihydropyridin-1-yl)acetic acid (25).** Ester **21** (3.59 g, 19.8 mmol) and EtOH : H<sub>2</sub>O (1 : 1, 60 mL) were added to a 250 mL oven-dried flask with stir bar and cooled to 0 °C. A 1 N aqueous solution of LiOH (40 mL, 40 mmol) was added and the solution was stirred for 2 h at 20 °C. After 2 h, ethanol

was removed under vacuum and 2 M HCl was added to the aqueous solution to reach a pH ~ 6. Next, the solution was concentrated down to dryness and the crude solid was dissolved with DCM and purified *via* flash chromatography (50 g SiO<sub>2</sub>, 0–10% MeOH/DCM w/0.1% formic acid) to afford **25** as a white powder (2.04 g, 67%). This compound has been previously reported and characterized (CAS# 56546-36-2).<sup>30</sup> <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>) δ 7.62–7.60 (m, 1H), 7.46–7.42 (m, 1H), 6.41–6.25 (m, 1H), 6.26–6.21 (m, 1H), 4.71 (s, 2H).

**[2-(Diethylamino)ethyl][(4-methoxyphenyl)methyl]amine (26b).** *N,N*-Diethylethylenediamine (1.25 g, 10.6 mmol) was added to a 100 mL oven-dried flask with stir bar and sealed under N<sub>2</sub>. *i*-PrOH (25 mL) was added and the flask was cooled to 0 °C. Then, *p*-anisaldehyde (1.58 mL, 12.8 mmol) was added dropwise, and the reaction was slowly warmed to 20 °C and stirred for 16 h. MeOH (20 mL) was added, the solution was cooled to 0 °C, and NaBH<sub>4</sub> (1.69 g, 44.7 mmol) was added in portions over 1 h. The solution was stirred for an additional 1 h, while warmed to 20 °C. A solution of 10% NaOH in H<sub>2</sub>O (25 mL) was added and the resulting mixture was extracted with DCM (3 × 40 mL). The combined organic layers were washed with a 10% aqueous solution of NaI (50 mL). The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The resulting crude yellow oil was dissolved in DCM (5 mL) and ether (10 mL), cooled to 0 °C, and a 4 M HCl solution in 1,4-dioxane (5.6 mL, 22.4 mmol) was added dropwise. The white precipitate was filtered and washed with DCM and diethyl ether to yield an off-white solid. This was dissolved in water (30 mL), cooled to 0 °C, and the solution was basified with NaOH (to pH ~ 9). The resulting mixture was extracted with DCM (3 × 40 mL). The combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to yield amine **26b** as a yellow oil (1.86 g, 74% yield). This compound has been previously reported (CAS# 65875-40-3).<sup>42</sup> *R*<sub>f</sub> = 0.57 (9 : 1 DCM : MeOH); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 2H), 2.66 (t, *J* = 6.2 Hz, 2H), 2.55 (t, *J* = 6.2 Hz, 2H), 2.49 (q, *J* = 7.1 Hz, 4H), 0.99 (t, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 158.6, 132.8, 129.3, 113.8, 55.3, 53.5, 52.7, 47.1, 46.9, 11.9; LC-MS *t*<sub>R</sub> = 0.89; *m/z* = 236.90 (M + H).

***N*-[2-(Diethylamino)ethyl]-2-(2-oxo-1,2-dihydropyridin-1-yl)acetamide (27a).** Carboxylic acid **25** (37.0 mg, 0.242 mmol) was added to an oven-dried 50 mL flask with stir bar and sealed under N<sub>2</sub>. To the suspension, anhydrous DCM (4.0 mL), HOBt (69.4 mg, 0.363 mmol), DIPEA (62.0 μL, 0.362 mmol), and *N,N*-diethylethylenediamine (33.7 mg, 0.290 mmol) were sequentially added. The reaction mixture was stirred for 5 min at 20 °C before EDC-HCl (69.4 mg, 0.362 mmol) was added in one portion. The reaction mixture was stirred at 20 °C for 48 h. Monitoring *via* LC-MS showed conversion to the desired product. The solvent was removed under vacuum and the residue was dry loaded using celite and purified *via* flash chromatography (12 g C18, 0–95% MeOH/H<sub>2</sub>O gradient w/ 0.1% NH<sub>4</sub>OH) to yield amide **27a** as a pale yellow oil (21 mg, 35%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.38–7.38 (m, 2H), 6.61 (d, *J* = 9.0 Hz, 1H), 6.24 (td, *J* = 1.3, 6.7 Hz, 1H), 4.56 (s, 2H), 3.30 (q, *J* = 5.7 Hz, 2H), 2.57–2.50 (m, 7H), 0.99 (t, *J* = 7.1 Hz, 6H);

$^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  168.1, 163.6, 141.5, 139.8, 139.7, 119.3, 107.2, 52.0, 51.2, 46.9, 36.6, 10.3; LC-MS  $t_{\text{R}}$  = 0.99;  $m/z$  = 251.80 ( $\text{M} + \text{H}$ ).

***N*-[2-(Diethylamino)ethyl]-*N*-[(4-methoxyphenyl)methyl]-2-(2-oxo-1,2-dihydropyridin-1-yl)acetamide (27b).** Carboxylic acid **25** (0.300 g, 19.6 mmol) was added to an oven dried 50 mL flask with stir bar and sealed under  $\text{N}_2$ . Anhydrous DCE (20.0 mL) was added, and the resulting mixture was cooled to 0 °C using an ice bath before EDC-HCl (0.563, 29.4 mmol), amine **27b** (0.300 g, 19.6 mmol), and DMAP (23.9 mg, 1.96 mmol) were added. The reaction was allowed to warm up to 20 °C and stirred under  $\text{N}_2$  for 16 h. The resulting solution was washed with 1 M NaOH (10 mL). The aqueous layer was extracted with DCM ( $2 \times 5$  mL), and the combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude yellow oil was dissolved with DCM and purified *via* flash chromatography (12 g C18, 0–95% MeOH/ $\text{H}_2\text{O}$  with 0.1%  $\text{NH}_4\text{OH}$ ) to yield amide **27b** as a colorless oil (213 mg, 29%). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR are complicated due to rotamers.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39–7.24 (m, 3H), 7.20–7.18 (m, 1H), 6.93–6.91 (m, 1H), 6.85–6.82 (m, 1H), 6.58–6.54 (m, 1H), 6.22–6.16 (m, 1H), 4.89 (s, 1H), 4.73 (s, 1H), 4.66 (s, 1H), 4.59 (s, 1H), 3.80–3.77 (s, 3H), 3.46–3.37 (m, 2H), 2.64–2.45 (m, 6H), 1.03–0.95 (m, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  167.0, 166.7, 162.5, 162.4, 159.2, 159.0, 140.0, 140.0, 138.9, 138.7, 129.5, 129.1, 128.2, 127.9, 120.4, 114.3, 114.0, 105.8, 105.7, 55.3, 55.2, 51.5, 51.3, 50.3, 49.7, 49.4, 48.9, 47.5, 47.4, 45.6, 45.3, 45.2, 12.0; LC-MS  $t_{\text{R}}$  = 1.43;  $m/z$  = 371.95 ( $\text{M} + \text{H}$ ).

**Benzyl 2-bromo-3-hydroxy-3-phenylpropanoate (35a).** To a 25 mL flask with stir bar, benzyl cinnamate (477 mg, 2.00 mmol), NBS (427 mg, 2.40 mmol) and  $\text{MeCN}:\text{H}_2\text{O}$  (4 : 1) (10 mL) were added and the solution was cooled to 0 °C. Iodine (50.8 mg, 0.200 mmol) was added and the mixture was stirred for 72 h. The reaction mixture was washed with 10% aq. sodium thiosulfate (20 mL) and extracted with EtOAc ( $3 \times 40$  mL). The combined organic extracts were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was dissolved in DCM and purified by flash chromatography (50 g  $\text{SiO}_2$ , 0–100% EtOAc/hexanes) to afford bromohydrin **35a** as a colorless liquid (276 mg, 41%). This compound has been previously reported (CAS# 1332928-50-3).<sup>43</sup>  $R_{\text{f}}$  = 0.47 (50 : 50 EtOAc : hexanes);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.23–7.37 (m, 10H), 5.20 (s, 2H), 5.07 (dd,  $J$  = 5.5, 8.2 Hz, 1H), 4.41 (d,  $J$  = 8.2 Hz, 1H), 3.26 (br d,  $J$  = 5.5 Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  169.3, 139.0, 134.9, 128.9, 128.7, 128.7, 128.3, 127.0, 75.3, 68.0, 47.8.

**Methyl 2-bromo-3-hydroxy-3-phenylpropanoate (35b).** The procedure for the synthesis of bromohydrin **35a** was used with the following modifications: methyl *trans*-cinnamate (1.62 g, 10.0 mmol) was used instead of benzyl *trans*-cinnamate, NBS (2.14 g, 12.0 mmol),  $\text{MeCN}:\text{H}_2\text{O}$  (4 : 1) (50 mL), and iodine (254 mg, 1.00 mmol). The crude product was dissolved in DCM and purified by flash chromatography (100 g  $\text{SiO}_2$ , 0–40% EtOAc/hexanes) to afford bromohydrin **35b** as an off-white solid (1.45 g, 56%). This compound has been previously

reported (CAS# 90841-69-3).<sup>31</sup>  $R_{\text{f}}$  = 0.38 (70 : 30 hexanes : EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.38 (m, 5H), 5.06 (dd,  $J$  = 5.3, 8.4 Hz, 1H), 4.37 (d,  $J$  = 8.4 Hz, 1H), 3.79 (s, 3H), 3.28 (d,  $J$  = 5.3 Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 139.0, 128.9, 128.7, 127.1, 75.3, 53.3, 47.5.

**Benzyl 3-phenyloxirane-2-carboxylate (36).** In a 4 mL oven-dried vial with stir bar, a suspension of 2-hydroxypyridone (6.8 mg, 0.072 mmol), tetrabutylammonium bromide (1.9 mg, 0.0060 mmol), and ground potassium carbonate (24.7 mg, 0.179 mmol) in acetone (0.5 mL) was heated at 40 °C for 30 min. A solution of the bromohydrin **35a** (20.0 mg, 0.0597 mmol) in acetone (0.2 mL) was added dropwise over 5 min and the mixture was stirred at 40 °C for 30 min. The reaction mixture was monitored *via* LCMS and TLC (50 : 50 EtOAc : hexanes) and stained with PAA. Saturated  $\text{NH}_4\text{Cl}$  (1 mL) and  $\text{H}_2\text{O}$  (1 mL) were added the solution was stirred for 10 min. The resulting solution was diluted with  $\text{H}_2\text{O}$  (5 mL) and extracted with DCM ( $3 \times 10$  mL). The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude pale yellow oil was dissolved in DCM and purified by flash chromatography (5 g  $\text{SiO}_2$ , 0–100% EtOAc/hexanes) to yield pyridone **36** as a colorless oil (11.4 mg, 75%). This compound has been previously reported and synthesized (CAS# 144667-57-2).<sup>44</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.55 (d,  $J$  = 1.7 Hz, 1H), 4.11 (d,  $J$  = 1.7 Hz, 1H), 5.25 (m, 2H), 7.25–7.40 (m, 10H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  168.2, 135.1, 135.0, 129.2, 128.8, 128.8, 128.7, 126.0, 67.6, 58.2, 56.9.

**Methyl 2-bromo-3-[(*tert*-butyldimethylsilyl)oxy]-3-phenylpropanoate (37a).** Bromohydrin **35a** (70.0 mg, 0.209 mmol) was added to a 4 mL oven-dried vial with stir bar and sealed under  $\text{N}_2$ . Anhydrous DCM (1.0 mL), 2,6-lutidine (92.0  $\mu\text{L}$ , 0.794 mmol) and TBSOTf (72.0  $\mu\text{L}$ , 0.314 mmol) were sequentially added and the solution was stirred at 20 °C for 2 h. TLC analysis (50 : 50 EtOAc : hexanes) indicated consumption of starting material. The reaction was quenched with the slow addition of saturated NaCl (2 mL), and the mixture was stirred for 15 min. The aqueous layer was extracted with ether ( $2 \times 10$  mL), and the organic layer was washed with brine (5 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and condensed. The crude yellow oil was dissolved in DCM and purified by flash chromatography (25 g  $\text{SiO}_2$ , 0–20% EtOAc/hexanes) to yield **37a** as a pale yellow oil (277 mg, 77%).<sup>45</sup> This compound has been previously reported and synthesized (CAS# 175722-72-2).  $R_{\text{f}}$  = 0.68 (70 : 30 hexanes : EtOAc);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31–7.38 (m, 5H), 4.98 (d,  $J$  = 9.8 Hz, 1H), 4.21 (d,  $J$  = 9.8 Hz, 1H), 3.81 (s, 3H), 0.79 (s, 9H), 0.01 (s, 3H), –0.29 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  169.6, 140.1, 128.7, 127.7, 76.7, 53.0, 49.4, 25.6, 18.0, –4.7, –3.3.

**Methyl 2-bromo-3-(methoxymethoxy)-3-phenylpropanoate (37b).** Bromohydrin **35a** (100 mg, 0.386 mmol) was added to a 4 mL oven-dried vial with stir bar and sealed under  $\text{N}_2$ . Anhydrous DCM (1.0 mL) was added and the solution was cooled to 0 °C. Then, 2,6-lutidine (67.4  $\mu\text{L}$ , 0.579 mmol) was added followed by dropwise addition of methoxychloromethane (44  $\mu\text{L}$ , 0.579 mmol). The solution was stirred at 0 °C



for 1 h and allowed to warm up to room temperature, then stirred at room temperature for 16 h under N<sub>2</sub>. After 16 h, the reaction was diluted with EtOAc (15 mL) and washed with saturated aq. NaHCO<sub>3</sub> (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude yellow oil was dissolved in DCM and purified by flash chromatography (5 g SiO<sub>2</sub>, 0–40% EtOAc/hexanes) to yield **37b** as a colorless oil (78 mg, 66%). *R*<sub>f</sub> = 0.59 (70 : 30 hexanes : EtOAc); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.40–7.35 (m, 5H), 5.00 (d, *J* = 10.1 Hz, 1H), 4.54–4.45 (m, 2H), 4.33 (d, *J* = 10.1 Hz, 1H), 3.85 (s, 3H), 3.25 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 169.4, 136.9, 129.1, 128.7, 128.6, 128.4, 128.4, 127.1, 94.8, 78.7, 56.1, 53.1, 47.3.

**Methyl 3-(acetyloxy)-2-bromo-3-phenylpropanoate (39).** Bromohydrin **35b** (3.28 g, 12.6 mmol) was added to a 50 mL oven-dried flask with stir bar and sealed under N<sub>2</sub>. Anhydrous DCM (20.0 mL), acetic anhydride (1.34 mL, 14.3 mmol) and DMAP (61.8 mg, 0.506 mmol) were sequentially added. The solution was stirred at 20 °C for 16 h. TLC analysis (50 : 50 hexanes : EtOAc) confirmed consumption of starting material. The reaction mixture was poured into ice cold H<sub>2</sub>O (100 mL), and extracted with DCM (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude pale yellow oil was dissolved in DCM and purified by flash chromatography (100 g SiO<sub>2</sub>, 0–20% EtOAc/hexanes) to yield **39** as a colorless oil (3.55 g, 93%). This compound has been previously reported and synthesized (CAS# 59339-56-9).<sup>46</sup> *R*<sub>f</sub> = 0.73 (50 : 50 EtOAc : hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.43–7.35 (m, 5H), 6.11 (d, *J* = 9.9 Hz, 1H), 4.50 (d, *J* = 9.9 Hz, 1H), 3.81 (s, 3H), 2.02 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 168.8, 168.3, 136.0, 129.3, 128.6, 128.0, 75.6, 53.3, 46.1, 20.9.

**Methyl 2-(acetyloxy)-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (40b).** 2-Hydroxypyridine (3.55 g, 37.4 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (8.11 g, 24.9 mmol) were added to a 250 mL oven-dried flask with stir bar and sealed under N<sub>2</sub>. Anhydrous DMF (75 mL) was added and the suspension was heated at 50 °C for 1 h, then cooled to 20 °C. A solution of alkyl bromide **39** (7.50 g, 24.9 mmol) in anhydrous DMF (20 mL) was added and the reaction mixture was stirred at 20 °C for 16 h. The reaction was quenched with saturated aq. NH<sub>4</sub>Cl (75 mL), diluted with EtOAc (500 mL), and washed with H<sub>2</sub>O (6 × 200 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The resulting crude yellow oil was dissolved in DCM and purified by flash chromatography (100 g SiO<sub>2</sub>, 0–100% EtOAc/hexanes) to yield **40b** as a waxy off-white solid (1.98 g, 25%) and **41b** as an off-white solid (0.60 g, 9%). **40b**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.49–7.47 (m, 2H), 7.39–7.38 (m, 3H), 7.27–7.25 (m, 1H), 7.05 (d, *J* = 7.1 Hz, 1H), 6.87 (d, *J* = 5.1 Hz, 1H), 6.60 (d, *J* = 9.7 Hz, 1H), 6.02 (t, *J* = 6.7 Hz, 1H), 5.89 (d, *J* = 7.1 Hz, 1H), 3.65 (s, 3H), 2.14 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.4, 167.9, 162.2, 139.4, 135.9, 134.6, 129.5, 129.3, 129.1, 120.7, 105.8, 71.3, 57.2, 53.0, 20.7; LC-MS *t*<sub>R</sub> = 5.50; *m/z* = 255.75 (M + H). **41b**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.47–7.40 (m, 7H), 7.10 (ddd, *J* = 6.8, 2.1, 0.7 Hz, 1H),

6.66–6.63 (m, 2H), 6.27 (td, *J* = 6.8, 1.2 Hz, 1H), 3.69 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 164.0, 161.8, 151.1, 140.6, 137.5, 131.2, 129.5, 129.2, 126.6, 122.1, 115.8, 105.9, 52.0; LC-MS *t*<sub>R</sub> = 4.25; *m/z* = 255.75 (M + H).

**2-Hydroxy-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoic acid (42b).** To a 50 mL flask with stir bar, acetate **40b** (1.98 g, 6.28 mmol), THF (48 mL), H<sub>2</sub>O (12 mL), and LiOH·H<sub>2</sub>O (580 mg, 13.8 mmol) were sequentially added and the reaction was stirred at 20 °C for 30 min. Analysis *via* LC-MS indicated complete conversion. THF was removed under vacuum before a 1 M HCl solution was added dropwise until the pH reached ~1. The solution was concentrated, the crude product was dry loaded using celite, and purified *via* flash chromatography (12 g C18, 0–95% 0.5 N NH<sub>3</sub> in MeOH/H<sub>2</sub>O) to afford carboxylic acid **42b** as an off-white solid (1.49 g, 92%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.49–7.47 (m, 3H), 7.37–7.29 (m, 4H), 6.43–6.40 (m, 2H), 6.15 (t, *J* = 6.7 Hz, 1H), 4.66 (d, *J* = 5.0 Hz, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 173.2, 161.2, 139.7, 137.6, 136.8, 129.3, 128.6, 128.1, 119.2, 105.0, 70.4, 58.2; LC-MS *t*<sub>R</sub> = 3.34; *m/z* = 258.05 (M – H).

**(2-Aminoethoxy)(tert-butyl)dimethylsilane (44).** Ethanolamine (2.07 g, 33.9 mmol) was added to a 25 mL oven-dried flask with stir bar and sealed under N<sub>2</sub>. Imidazole (4.61 g, 67.8 mmol) and anhydrous DCM (30 mL) were added before a solution of TBSCl (5.11 g, 33.9 mmol) in anhydrous DCM (5 mL) was added dropwise over 10 min *via* syringe pump at 20 °C. The solution was allowed to stir at room temperature for 1 h. Next, the solution was diluted with DCM (150 mL) and washed with water (3 × 50 mL) and brine (50 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated to give amine **44** as a pale yellow oil (4.77 g, 80%). This compound has been previously reported and synthesized (CAS# 101711-55-1).<sup>47</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 3.63 (t, *J* = 5.2 Hz, 2H), 2.77 (t, *J* = 5.2 Hz, 2H), 1.47, (br s, 2H), 0.91 (s, 9H), 0.07 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 65.5, 44.5, 26.1, 18.5, –5.2.

**N-2-[(tert-Butyldimethylsilyl)oxy]ethyl-2-hydroxy-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (46).** To an oven-dried 50 mL round bottom flask, acid **42** (420 mg, 1.62 mmol), amine **44** (568 mg, 3.24), anhydrous DMF (10 mL), and anhydrous DCE (10 mL) were added. Next, NMM (356 μL, 3.24 mmol) was added *via* syringe and HATU (739 mg, 1.94 mmol) was added in one portion. The reaction mixture was stirred at 20 °C for 16 h under N<sub>2</sub>. After 16 h, the reaction mixture was diluted with EtOAc (200 mL) and washed with H<sub>2</sub>O (2 × 50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and condensed under vacuum to yield a crude yellow oil. The crude oil was purified by flash chromatography (25 g SiO<sub>2</sub>, 0–100% EtOAc/hexanes) to afford amide **46** as a colorless oil (620 mg, 91%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.44–7.40 (m, 1H), 7.35–7.30 (m, 7H), 6.81 (br s, 1H), 6.68 (d, *J* = 9.1 Hz, 1H), 6.25 (t, *J* = 7.3 Hz, 1H), 6.00 (s, 1H), 4.84 (s, 1H), 3.66–3.53 (m, 2H), 3.42–3.30 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.9, 164.9, 140.6, 139.2, 135.0, 128.7, 128.6, 128.4, 121.6, 107.7, 74.5, 71.5, 61.8, 41.6, 26.0, 18.4, –5.3; LC-MS *t*<sub>R</sub> = 5.74; *m/z* = 417.00 (M + H).



***N*-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-2-oxo-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (47).** Alcohol 46 (205 mg, 0.492 mmol) was added to a 20 mL oven-dried vial with stir bar and sealed under N<sub>2</sub>. Anhydrous DCM (10 mL) and DMP (251 mg, 0.592 mmol) were added and the reaction was stirred at 20 °C for 2 h under N<sub>2</sub>. A 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous solution (10 mL) was added and the biphasic mixture was stirred for 20 min until the two layers became clear. The aqueous layer was separated and the organic layer was washed with saturated NaHCO<sub>3</sub> (2 × 5 mL). The combined aqueous layers were extracted with EtOAc (1 × 10 mL) and the combined organics were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude oil was dissolved in DCM and purified *via* flash chromatography (25 g SiO<sub>2</sub>, 0–80% EtOAc/hexanes) to afford ketone 47 as an off-white solid (170 mg, 83%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.38–7.26 (m, 7H), 6.93 (d, *J* = 7.0 Hz, 1H), 6.85 (s, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 6.08 (t, *J* = 6.7 Hz, 1H), 3.64–3.60 (m, 2H), 3.43–3.25 (m, 2H), 0.80 (s, 9H), −0.04 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 189.8, 162.4, 159.4, 140.2, 135.5, 130.7, 130.2, 130.0, 129.7, 119.7, 106.5, 64.3, 61.3, 41.5, 25.9, 18.2, −5.4; LC-MS *t*<sub>R</sub> = 6.09; *m/z* = 414.95 (M + H).

***N*-(2-Hydroxyethyl)-2-oxo-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (48).** To a 100 mL flask charged with a stir bar, silyl ether 47 (100 mg, 0.241 mmol) and MeOH (10.0 mL) were added. Then a 2% aqueous HCl in MeOH solution (10.0 mL) was added, and the reaction was stirred for 1 h at 20 °C. The solution was concentrated, dry loaded on to celite, and purified *via* flash chromatography (12 g C18, 0–40% MeOH/H<sub>2</sub>O) to afford alcohol 48 as a colorless oil (56.7 mg, 78%). LC-MS *t*<sub>R</sub> = 3.64; *m/z* = 300.85 (M + H). This intermediate was used directly in the next step.

**Diethyl({2-[2-oxo-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamido]ethyl})azanium chloride (50).** Alcohol 48 (40.0 mg, 0.133 mmol) was added to a 20 mL oven-dried vial with stir bar and sealed under Ar. Anhydrous MeCN (4.0 mL), DIPEA (22.8 μL, 0.133 mmol), and MsCl (30.9 μL, 0.400 mmol) were respectively added and the solution was stirred at 20 °C for 24 h. Analysis *via* TLC confirmed conversion to the mesylate. Diethylamine (275 μL, 2.66 mmol) was added and the reaction was heated at 70 °C for 16 h under Ar. The reaction was concentrated, dry loaded using celite, and purified *via* flash chromatography (10 g C18, MeOH/H<sub>2</sub>O gradient w/0.1% formic acid) to afford the free base of amine 50 as an off-white powder (11.0 mg, 28%). *R*<sub>f</sub> = 0.61 (95 : 5 DCM : MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.61 (s, 1H), 8.03 (s, 1H), 7.51–7.49 (m, 3H), 7.41 (ddd, *J* = 8.8, 6.6, 1.9 Hz, 1H), 7.37–7.35 (m, 2H), 6.90 (dd, *J* = 7.1, 1.7 Hz, 1H), 6.55 (d, *J* = 8.8 Hz, 1H), 6.15 (td, *J* = 6.6, 1.2 Hz, 1H), 6.07 (s, 1H), 4.73–4.70 (m, 1H), 4.26–4.22 (m, 1H), 3.86–3.58 (m, 6H), 1.36–1.24 (m, 6H). This compound had poor solubility in chloroform and MeOH. The HCl salt was formed prior to <sup>13</sup>C NMR analysis. The product was taken up into minimal H<sub>2</sub>O and 0.5 mL of 1 M HCl was added. The solution was lyophilized to afford a yellow oil. <sup>13</sup>C NMR (75 MHz, D<sub>2</sub>O) δ 170.4, 164.2, 155.1, 143.0, 136.5, 131.0, 131.0, 130.4, 129.9, 129.8, 118.9, 109.2, 64.8, 64.6, 49.7, 45.5, 41.9, 13.3, 10.6; LC-MS *t*<sub>R</sub> = 1.61; *m/z* = 356.40 (M + H).

**Ethyl 2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (51).** In a 20 mL oven-dried vial with stir bar, HMDS (1.90 mL, 9.11 mmol) and anhydrous THF (9.0 mL) were added under N<sub>2</sub>. The solution was cooled to 0 °C in an ice bath before *n*-butyl lithium (5.43 mL of a 1.6 M solution in hexanes, 8.69 mmol) was added dropwise over 10 min. The solution was cooled to −78 °C before a solution of ester 21 (1.50 g, 8.28 mmol) in anhydrous THF (25.0 mL) was added dropwise. The solution was stirred at −78 °C for 1 h under N<sub>2</sub> before benzylbromide (985 μL, 8.28 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm up to 0 °C, quenched with saturated NH<sub>4</sub>Cl (10 mL), and diluted with EtOAc (50 mL). The organic layer was separated, washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude material was dissolved in DCM and purified *via* flash chromatography (100 g SiO<sub>2</sub>, 0–40% EtOAc/hexanes) to afford 51 as a colorless oil (1.52 g, 68%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.28–7.18 (m, 4H), 7.11–7.08 (m, 2H), 7.03 (dd, *J* = 6.9, 1.5 Hz, 1H), 6.50 (d, *J* = 9.2 Hz, 1H), 6.03 (td, *J* = 6.8, 1.3 Hz, 1H), 5.41 (dd, *J* = 9.7, 5.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.50 (m, 1H), 3.33 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 169.5, 162.2, 139.6, 136.5, 136.1, 129.1, 128.7, 127.1, 120.8, 105.6, 61.9, 61.2, 36.3, 14.1; LC-MS *t*<sub>R</sub> = 4.67; *m/z* = 271.90 (M + H).

**Ethyl (2Z)-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylprop-2-enoate (53).** The procedure for the synthesis of 51 was followed using HMDS (392 mg, 2.43 mmol), anhydrous THF (9.0 mL), *n*-butyl lithium (1.45 mL of a 1.6 M solution in hexanes, 2.32 mmol), 21 (400 mg, 2.21 mmol) in anhydrous THF (3.0 mL), and benzaldehyde (0.247 mL, 2.43 mmol) instead of benzylbromide. After workup, the product was dissolved in DCM and purified *via* flash chromatography (25 g SiO<sub>2</sub>, 0–50% EtOAc/hexanes) to afford alkene 53 as an off-white solid (272 mg, 46%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.83 (s, 1H), 7.43 (ddd, *J* = 9.0, 6.6, 2.0 Hz, 1H), 7.33–7.26 (m, 3H), 7.20–7.18 (m, 2H), 6.96 (dd, *J* = 6.7, 1.8 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 6.18 (td, *J* = 6.7, 1.0 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.4, 162.4, 140.8, 137.7, 137.4, 131.4, 130.5, 130.2, 129.9, 128.9, 121.8, 106.8, 62.0, 14.1. LC-MS *t*<sub>R</sub> = 6.06; *m/z* = 269.80 (M + H).

**(2Z)-2-(2-Oxo-1,2-dihydropyridin-1-yl)-3-phenylprop-2-enoic acid (54).** To a 15 mL flask with stir bar, ester 53 (136 mg, 0.504 mmol), THF (6.0 mL), H<sub>2</sub>O (1.5 mL), and LiOH·H<sub>2</sub>O (25.4 mg, 0.604 mmol) were added and the solution was stirred at 20 °C for 12 h. THF was removed under vacuum before a 1 M HCl solution was added dropwise until the pH reached ~1. The solution was concentrated under vacuum and the crude product was dry loaded using celite and purified *via* flash chromatography (12 g C18, 0–75% MeOH/H<sub>2</sub>O w/0.1% formic acid) to afford carboxylic acid 54 as an off-white solid (108 mg, 89%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.94 (s, 1H), 7.65 (ddd, *J* = 9.1, 6.7, 2.0 Hz, 1H), 7.39–7.30 (m, 4H), 7.20–7.18 (m, 2H), 6.67 (d, *J* = 9.1 Hz, 1H), 6.42 (td, *J* = 6.7, 1.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD) δ 166.2, 164.8, 143.6, 140.0, 139.0, 133.1, 131.7, 131.6, 130.9, 130.1, 121.6, 109.4; LC-MS *t*<sub>R</sub> = 4.17; *m/z* = 241.75 (M + H).

**Ethyl 3-hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (55).** In a 100 mL oven-dried flask with stir bar, diisopropylamine (309  $\mu$ L, 2.21 mmol) and anhydrous THF (35.0 mL) were added *via* syringe under  $N_2$ . The solution was cooled to  $-78^\circ\text{C}$  in a dry ice/acetone bath before *n*-butyl lithium (1.38 mL of a 1.6 M solution in hexanes, 2.21 mmol) was added dropwise over 10 min. The solution was allowed to stir for 30 min before a solution of **21** (400 mg, 2.21 mmol) in anhydrous THF (3.0 mL) was added dropwise over 5 min. The heterogeneous solution was stirred at  $-78^\circ\text{C}$  for 1 h before benzaldehyde (0.247 mL, 2.43 mmol) was added, and the solution was stirred at  $-78^\circ\text{C}$  for 2 h. The reaction was quenched at  $-78^\circ\text{C}$  *via* the addition saturated aq.  $NH_4Cl$  (15 mL) and diluted with EtOAc (75 mL). The organic layer was separated, washed with brine, dried over anhydrous  $Na_2SO_4$ , filtered, and concentrated. The crude material was dissolved in DCM and purified *via* flash chromatography (50 g  $SiO_2$ , 0–100% EtOAc/hexanes) to afford alcohol **55** as a colorless oil (307 mg, 48%). The NMR spectra are complex due to diastereomers.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.59 (dd,  $J$  = 6.8, 1.3 Hz, 1H), 7.26–7.15 (m, 12H), 6.80 (dd,  $J$  = 6.8, 1.5 Hz, 1H), 6.39 (d,  $J$  = 9.1 Hz, 1H), 6.28 (d,  $J$  = 9.1 Hz, 1H), 6.05 (td,  $J$  = 6.7, 1.2 Hz, 1H), 5.86 (td,  $J$  = 6.7 Hz, 1.2 Hz, 1H), 5.81 (d,  $J$  = 4.3 Hz, 1H), 5.63 (d,  $J$  = 4.3 Hz, 1H), 5.45 (d,  $J$  = 7.5 Hz, 1H), 4.74 (d,  $J$  = 7.5 Hz, 1H), 4.22–4.16 (m, 4H), 1.24–1.19 (m, 6H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  169.4, 168.2, 162.9, 162.3, 140.2, 140.1, 139.5, 138.9, 138.5, 137.9, 128.4, 128.3, 127.8, 126.4, 125.9, 120.3, 119.7, 105.9, 105.6, 73.5, 72.1, 67.5, 63.5, 62.1, 62.1, 60.4, 21.1, 14.2, 14.1, 14.0; LC-MS  $t_R$  = 4.78, 4.92;  $m/z$  = 287.80 ( $M + H$ ).

**Ethyl 3-[(*tert*-butyldimethylsilyl)oxy]-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (56).** The procedure for the synthesis of **37a** was used with the following modifications: **55** (153 mg, 0.533 mmol), DCM (6.0 mL), 2,6-lutidine (74.4  $\mu$ L, 0.639 mmol) and TBSOTf (147  $\mu$ L, 0.639 mmol) were used. The crude oil was dissolved in DCM and purified *via* flash chromatography (25 g  $SiO_2$ , 0–50% EtOAc/hexanes) to yield **56** as a pale yellow oil (187 mg, 87%).  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  8.20 (dd,  $J$  = 6.9, 1.4 Hz, 1H), 7.87 (dd,  $J$  = 6.9, 1.4 Hz, 1H), 7.56–7.38 (m, 11H), 6.62 (d,  $J$  = 9.2 Hz, 1H), 6.53 (d,  $J$  = 9.2 Hz, 1H), 6.44–6.39 (m, 1H), 6.33–6.28 (m, 1H), 6.12 (d,  $J$  = 7.2 Hz, 1H), 5.87 (d,  $J$  = 3.9 Hz, 1H), 5.44 (d,  $J$  = 7.2 Hz, 1H), 4.59–4.51 (m, 1H), 4.45–4.33 (m, 3H), 1.53 (t,  $J$  = 7.1 Hz, 3H), 1.46 (t,  $J$  = 7.1 Hz, 3H), 1.13 (s, 9H), 1.11 (s, 9H), 0.29 (s, 3H), 0.25 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  169.0, 168.5, 162.2, 161.8, 139.6, 139.5, 139.4, 139.3, 138.7, 136.6, 128.3, 128.2, 128.2, 128.2, 127.0, 126.4, 120.4, 119.7, 105.4, 104.5, 75.6, 75.4, 62.1, 61.9, 61.7, 61.5, 25.8, 25.8, 18.1, 18.1, 14.2, 14.1,  $-4.4$ ,  $-4.6$ ,  $-5.3$ ,  $-5.5$ ; LC-MS  $t_R$  = 6.95;  $m/z$  = 401.95 ( $M + H$ ).

**Prop-2-en-1-yl 2-(2-oxo-1,2-dihydropyridin-1-yl)acetate (57).** NaH (60% dispersion in mineral oil, 1.77 g, 46.3 mmol) was added to a 500 mL oven-dried flask with stir bar and sealed under  $N_2$ . Anhydrous DMF (125 mL) was added and the suspension was cooled to  $0^\circ\text{C}$  in an ice bath. A solution of 2-hydroxypyridine (4.00 g, 42.1 mmol) in anhydrous DMF (25.0 mL) was slowly added and stirred for 1 h at  $0^\circ\text{C}$ . Allyl

chloroacetate (5.98 mL, 50.5 mmol) was added and the mixture was stirred at  $20^\circ\text{C}$  for 12 h. The reaction was quenched with saturated  $NH_4Cl$  (200 mL) and diluted with EtOAc (750 mL). The organic layer was washed with water (6  $\times$  200 mL), dried over anhydrous  $Na_2SO_4$ , filtered, and concentrated. The crude product was dissolved in DCM and purified *via* flash chromatography (100 g  $SiO_2$ , 0–85% EtOAc/hexanes) to afford pyridone **57** as a pale yellow oil (3.40 g, 42%).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.30 (ddd,  $J$  = 9.2, 6.7, 2.1 Hz, 1H), 7.20 (ddd,  $J$  = 6.7, 2.1, 0.7 Hz, 1H), 6.49 (ddd,  $J$  = 9.2, 1.4, 0.7 Hz, 1H), 6.13 (td,  $J$  = 6.7, 1.4 Hz, 1H), 5.82 (ddt,  $J$  = 17.2, 10.5, 5.7 Hz, 1H), 5.25 (dq,  $J$  = 17.2 1.5 Hz, 1H), 5.17 (dq,  $J$  = 10.5, 1.3 Hz, 1H), 4.60 (s, 2H), 4.58 (dt,  $J$  = 5.7, 1.4 Hz, 2H).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  167.5, 162.4, 140.3, 138.0, 131.3, 121.0, 119.0, 106.2, 66.3, 50.5. LC-MS  $t_R$  = 2.30;  $m/z$  = 181.90 ( $M + H$ ).

**Prop-2-en-1-yl 3-hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (58).** In an oven-dried 100 mL flask with stir bar, anhydrous THF (50.0 mL) and diisopropylamine (1.55 mL, 11.0 mmol) were added *via* syringe under  $N_2$ . The solution was cooled to  $-78^\circ\text{C}$  before *n*-butyl lithium (6.90 mL of a 1.6 M solution in hexanes, 11.0 mmol) was added dropwise over 5 min. The solution was stirred for 30 min before a solution of ester **57** (1.94 g, 10.0 mmol) in anhydrous THF (8.0 mL) was added dropwise over 5 min and stirred at  $-78^\circ\text{C}$  for 1 h. Benzaldehyde (1.53 mL, 15.1 mmol) was added and the resulting solution was stirred at  $-78^\circ\text{C}$  for 2 h. The reaction was quenched at  $-78^\circ\text{C}$  with saturated aq.  $NH_4Cl$  and diluted with EtOAc (200 mL) and  $H_2O$  (10 mL). The layers were separated and the organic layer was washed with brine, dried over anhydrous  $Na_2SO_4$ , and concentrated. The crude yellow oil was dissolved in DCM and purified *via* flash chromatography (100 g  $SiO_2$ , 0–70% EtOAc/hexanes) to afford alcohol **58** as a yellow oil (2.45 g, 82%).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.43 (d,  $J$  = 7.9 Hz, 1H), 7.27–7.22 (m, 13H), 6.71 (dd,  $J$  = 6.8, 1.5 Hz, 1H), 6.46 (d,  $J$  = 9.1 Hz, 1H), 6.40 (d,  $J$  = 8.8 Hz, 1H), 6.09 (td,  $J$  = 6.8, 1.3 Hz, 1H), 5.94–5.81 (m, 3H), 5.73 (s, 2H), 5.57 (d,  $J$  = 7.9 Hz, 1H), 5.34–5.20 (m, 4H), 4.72–4.64 (m, 6H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  169.2, 167.9, 163.1, 162.4, 140.3, 140.2, 139.4, 138.7, 138.5, 137.9, 131.4, 131.3, 128.5, 128.4, 128.4, 128.0, 126.4, 125.9, 120.5, 120.0, 119.1, 119.0, 106.0, 105.8, 73.7, 72.1, 68.0, 66.6, 66.6, 64.0; LC-MS  $t_R$  = 4.40, 4.53;  $m/z$  = 299.75 ( $M + H$ ).

**3-Hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoic acid (59).** Alcohol **58** (1.90 g, 0.264 mmol) and  $Pd(PPh_3)_4$  (12.2 mg, 0.0106 mmol) were added to a 500 mL oven-dried flask with stir bar and sealed under  $N_2$ . Anhydrous THF (6.0 mL) and morpholine (24.2  $\mu$ L, 0.277 mmol) were added *via* syringe and the reaction was stirred at  $20^\circ\text{C}$  for 30 min. After 30 min, analysis *via* LC-MS indicated consumption of starting material. The reaction mixture was concentrated, dry loaded using celite, and purified using flash chromatography (30 g C18, 0–95% MeOH/ $H_2O$  w/0.1% formic acid) to afford carboxylic acid **59** as a yellow oil (1.20 g, 73%).  $^1H$  NMR (400 MHz,  $CD_3OD$ )  $\delta$  8.10 (d,  $J$  = 6.5 Hz, 1H), 7.44 (d,  $J$  = 6.5 Hz, 1H), 7.36–7.15 (m, 10H), 6.37 (d,  $J$  = 9.0 Hz, 1H), 6.30–6.27 (m, 1H), 6.14–6.10 (m, 1H), 5.73 (d,  $J$  = 3.8 Hz, 1H), 5.45 (d,  $J$  =

7.9 Hz, 1H), 5.30 (d,  $J$  = 7.9 Hz, 1H). LC-MS  $t_R$  = 3.74, 3.88;  $m/z$  = 259.75 ( $M + H$ ).

***N*-[2-(Diethylamino)ethyl]-3-hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (60).** Carboxylic acid **59** (886 mg, 3.42 mmol) was added to a 500 mL oven-dried flask with stir bar and sealed under  $N_2$ . Anhydrous DCM (150 mL), HATU (1.95 g, 5.13 mmol), DIPEA (655  $\mu$ L, 3.76 mmol), and *N*, *N*-diethylethylenediamine (624  $\mu$ L, 4.44 mmol) were sequentially added and the solution was stirred at 20 °C for 12 h. After 12 h, the reaction was concentrated under vacuum, dry loaded using celite, and purified *via* flash chromatography (30 g C18, 0–95% MeOH/ $H_2O$  w/0.1% formic acid) to afford amide **60** as an off-white waxy solid (918 mg, 75%). m.p. 75–77 °C;  $^1H$  NMR (400 MHz,  $CD_3OD$ )  $\delta$  7.44 (dd,  $J$  = 6.9, 1.5 Hz, 1H), 7.34 (ddd,  $J$  = 9.0, 6.7, 2.0 Hz, 1H), 7.28–7.26 (m, 2H), 7.24–7.19 (m, 3H), 6.36 (dd,  $J$  = 9.0, 0.6 Hz, 1H), 6.14 (td,  $J$  = 6.7, 1.3 Hz, 1H), 5.39 (d,  $J$  = 9.5 Hz, 1H), 5.19 (d,  $J$  = 9.5 Hz, 1H), 3.79–3.73 (m, 1H), 3.64–3.57 (m, 1H), 3.38–3.22 (m, 6H), 1.31 (t,  $J$  = 7.3 Hz, 6H);  $^{13}C$  NMR (100 MHz,  $CD_3OD$ )  $\delta$  171.8, 164.4, 142.5, 141.1, 140.0, 129.5, 129.4, 128.0, 120.5, 108.4, 73.4, 67.3, 53.0, 49.1, 35.7, 9.2. LC-MS  $t_R$  = 1.07, 1.32;  $m/z$  = 357.95 ( $M + H$ ).

***N*-[2-(Diethylamino)ethyl]-3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (61).** Alcohol **60** (47.5 mg, 0.133 mmol) was added to a 20 mL oven-dried vial with stir bar and sealed under  $N_2$ . Anhydrous DCM (6.0 mL) and DMP (84.5 mg, 0.199 mmol) were sequentially added and the reaction mixture was stirred at 20 °C for 1 h. After 1 h,  $H_2O$  (2.7  $\mu$ L, 0.15 mmol) was added *via* microsyringe. The reaction solution was stirred at room temperature for 48 h before being quenched with saturated  $Na_2S_2O_3$  (3 mL). The product was extracted with DCM (3  $\times$  10 mL) and concentrated. The crude product was dissolved in DCM and purified *via* flash chromatography (12 g  $SiO_2$ , 0–20% MeOH/DCM) to afford ketone **61** as an off-white solid (11.7 mg, 25%).  $R_f$  = 0.71 (80:20 DCM:MeOH); m.p. 124–129 °C;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.01 (d,  $J$  = 7.1 Hz, 2H), 7.65 (dd,  $J$  = 6.8, 1.7 Hz, 1H), 7.60–7.56 (m, 1H), 7.48–7.44 (m, 1H), 7.40–7.34 (m, 2H), 6.60 (d,  $J$  = 9.2 Hz, 1H), 6.24 (td,  $J$  = 6.8, 1.3 Hz, 1H), 3.39–3.28 (m, 2H), 2.57–2.48 (m, 6H), 0.96 (t,  $J$  = 7.2 Hz, 6H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  192.0, 165.2, 162.0, 140.7, 137.4, 135.0, 134.3, 129.1, 128.8, 119.9, 106.2, 61.6, 51.1, 46.7, 37.4, 11.5; LC-MS  $t_R$  = 1.57;  $m/z$  = 356.20 ( $M + H$ ).

### PDI assay protocol

The PDI-catalyzed reduction of insulin was assayed by measuring the increase in turbidity as detected at an optical density of 650 nm using a Spectramax M3 (Molecular Devices, Sunnyvale, CA). Compounds were assayed in a clear, flat-bottom, 96 well plate (Nunc-Immuno™ MicroWell™, Sigma-Aldrich cat# M0661-1CS), at a final volume of 100  $\mu$ L. The validation assay consisted of 400 nM of PDI in a solution containing 100 mM potassium phosphate (pH 7.4), 0.1 mM bovine insulin, 2 mM EDTA and 0.5 mM DTT (all purchased from Sigma Aldrich, St Louis, MO). Compounds were used at the concentrations indicated. The reaction was performed at 25 °C

for 1 h. For calculation of the  $IC_{50}$ , we used absorbance values recorded at 25 min, after insulin aggregation is first detectable in the vehicle control compared with the corresponding value at that time point for specimens containing the test compound. Assays were performed with  $n$  = 3, and concentration-response curves were plotted using GraphPad Prism, with error bars representing standard error of the mean (SEM).

### Crystallographic data

CCDC 2004020 and 2004021 (Scheme 9), 2004022 (Scheme 12), and 2004023 (Fig. 3) contain the supplementary crystallographic data for this paper.†

## Author contributions

Proposed synthetic routes: C. D., E. G. Synthesized and characterized compounds: E. G. Conducted the insulin reduction assay: C. S., L. L., R. F. Determined X-ray crystal structures: S. V. L. Wrote and edited the manuscript: E. G., C. D.

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## Notes

An initial version of this manuscript was posted to the preprint server ChemRxiv.<sup>21</sup>

## Conflicts of interest

There are no conflicts to declare.

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## References

- 1 F. Hatahet and L. W. Ruddock, Protein Disulfide Isomerase: A Critical Evaluation of Its Function in Disulfide Bond Formation, *Antioxid. Redox Signal.*, 2009, **11**(11), 2807–2850.
- 2 S. Xu, S. Sankar and N. Neamati, Protein Disulfide Isomerase: A Promising Target for Cancer Therapy, *Drug Discovery Today*, 2014, **19**(3), 222–240.



- 3 R. Flaumenhaft, Advances in Vascular Thiol Isomerase Function, *Curr. Opin. Hematol.*, 2017, **24**(5), 439–445.
- 4 J. Cho, B. C. Furie, S. R. Coughlin and B. Furie, A Critical Role for Extracellular Protein Disulfide Isomerase During Thrombus Formation in Mice, *J. Clin. Invest.*, 2008, **118**(3), 1123–1131.
- 5 C. Reinhardt, M.-L. von Brühl, D. Manukyan, L. Grahl, M. Lorenz, B. Altmann, S. Dlugai, S. Hess, I. Konrad, L. Orschiedt, N. Mackman, L. Ruddock, S. Massberg and B. Engelmann, Protein Disulfide Isomerase Acts as an Injury Response Signal that Enhances Fibrin Generation via Tissue Factor Activation, *J. Clin. Invest.*, 2008, **118**(3), 1110–1122.
- 6 R. Jasuja, F. H. Passam, D. R. Kennedy, S. H. Kim, L. van Hessem, L. Lin, S. R. Bowley, S. S. Joshi, J. R. Dilks, B. Furie, B. C. Furie and R. Flaumenhaft, Protein Disulfide Isomerase Inhibitors Constitute a New Class of Antithrombotic Agents, *J. Clin. Invest.*, 2012, **122**(6), 2104–2113.
- 7 K. Kim, E. Hahm, J. Li, L.-M. Holbrook, P. Sasikumar, R. G. Stanley, M. Ushio-Fukai, J. M. Gibbins and J. Cho, Platelet Protein Disulfide Isomerase is Required for Thrombus Formation but not for Hemostasis in Mice, *Blood*, 2013, **122**(6), 1052–1061.
- 8 R. H. Bekendam, P. K. Bendapudi, L. Lin, P. P. Nag, J. Pu, D. R. Kennedy, A. Feldenzer, J. Chiu, K. M. Cook, B. Furie, M. Huang, P. J. Hogg and R. Flaumenhaft, A Substrate-driven Allosteric Switch that Enhances PDI Catalytic Activity, *Nat. Commun.*, 2016, **7**, 12579.
- 9 J. I. Zwicker, B. L. Schlechter, J. D. Stopa, H. A. Liebman, A. Aggarwal, M. Puligandla, T. Caughey, K. A. Bauer, N. Kuemmerle, E. Wong, T. Wun, M. McLaughlin, M. Hidalgo, D. Neuberg, B. Furie and R. Flaumenhaft, Targeting Protein Disulfide Isomerase with the Flavonoid Isoquercetin to Improve Hypercoagulability in Advanced Cancer, *JCI Insight*, 2019, **4**(4), e125851.
- 10 C. Khodier, L. VerPlank, P. P. Nag, J. Pu, J. Wurst, T. Pilyugina, C. Dockendorff, C. N. Galinski, A. A. Scalise, F. Passam, L. v. Hessem, J. Dilks, D. R. Kennedy, R. Flaumenhaft, M. A. J. Palmer, S. Dandapani, B. Munoz and S. L. Schrieber, *Identification of ML359 as a Small Molecule Inhibitor of Protein Disulfide Isomerase*, 2013, <https://www.ncbi.nlm.nih.gov/books/NBK189925/>.
- 11 L. Claisen and K. Meyer, Ueber das Amid der Acetessigsäure, *Ber. Dtsch. Chem. Ges.*, 1902, **35**(1), 583–584.
- 12 U. S. Sørensen, E. Falch and P. Krosgaard-Larsen, A Novel Route to 5-Substituted 3-Isoxazolols. Cyclization of N, O-DiBoc  $\beta$ -Keto Hydroxamic Acids Synthesized via Acyl Meldrum's Acids, *J. Org. Chem.*, 2000, **65**(4), 1003–1007.
- 13 J. S. Witzeman and W. D. Nottingham, Transacetoacetylation with tert-butyl acetoacetate: synthetic applications, *J. Org. Chem.*, 1991, **56**(5), 1713–1718.
- 14 H. O. Kim, R. K. Olsen and O. S. Choi, Copper(I)-promoted Condensation of  $\alpha$ -amino Acids with  $\beta$ -keto Thio Esters: Synthesis of N-acylated L-leucine Derivatives Containing (S)-4-Hydroxy-5-methyl- and (S)-4-Hydroxy-2,5-dimethyl-3-oxohexanoic acid, *J. Org. Chem.*, 1987, **52**(20), 4531–4536.
- 15 R. V. Hoffmann and D. J. Huizenga, A Simple Synthesis of 2,3-Diketo Amides from 3-Keto Amides, *J. Org. Chem.*, 1991, **56**(22), 6435–6439.
- 16 M. J. García, F. Rebolledo and V. Gotor, Lipase-catalyzed Aminolysis and Ammonolysis of  $\beta$ -Ketoesters. Synthesis of Optically Active  $\beta$ -Ketoamides, *Tetrahedron*, 1994, **50**(23), 6935–6940.
- 17 P. Kumar and R. K. Pandey, A Facile and Selective Procedure for Transesterification of  $\beta$ -Keto Esters Promoted by Yttria-Zirconia Based Lewis Acid Catalyst, *Synlett*, 2000, (2), 251–253.
- 18 J. K. Vandavasi, C.-T. Hsiao, W.-P. Hu, S. S. K. Boominathan and J.-J. Wang, Silver(I)-Catalyzed Tandem Approach to  $\beta$ -Oxo Amides, *Eur. J. Org. Chem.*, 2015, (14), 3171–3177.
- 19 J. C. Gramain, R. Remuson and D. Vallee, Intramolecular Photoreduction of  $\alpha$ -keto Esters. Total Synthesis of (+)-Isoretronecanol, *J. Org. Chem.*, 1985, **50**(5), 710–712.
- 20 P. C. Kuzma, L. E. Brown and T. M. Harris, Generation of the Dianion of N-(Trimethylsilyl)acetamide and Reaction of the Dianion with Electrophilic Reagents, *J. Org. Chem.*, 1984, **49**(11), 2015–2018.
- 21 E. Greve, S. V. Lindeman and C. Dockendorff, Route Exploration and Synthesis of the Reported Pyridone-based PDI Inhibitor STK076545. ChemRxiv 2020, preprint, <https://chemrxiv.org/s/6abc28f65da179d85f7f>.
- 22 L. Chen, E. Doval Santos, J. Yu, S. O'Neill-Slawecki, M. Mitchell, S. Sakata and B. Borer, A Simple Preparation of a (Pyridonyl-1)propargylacetic Acid Derivative, *Org. Process Res. Dev.*, 2006, **10**(4), 838–840.
- 23 K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee and B. S. Safina, A Mild and Selective Method for the Hydrolysis of Esters with Trimethyltin Hydroxide, *Angew. Chem., Int. Ed.*, 2005, **44**(9), 1378–1382.
- 24 J. D. Goodreid, P. A. Duspara, C. Bosch and R. A. Batey, Amidation Reactions from the Direct Coupling of Metal Carboxylate Salts with Amines, *J. Org. Chem.*, 2014, **79**(3), 943–954.
- 25 R. E. Tirpak, R. S. Olsen and M. W. Rathke, Carboxylation of Ketones using Triethylamine and Magnesium Halides, *J. Org. Chem.*, 1985, **50**(24), 4877–4879.
- 26 H. Li, Z. He, X. Guo, W. Li, X. Zhao and Z. Li, Iron-Catalyzed Selective Oxidation of N-Methyl Amines: Highly Efficient Synthesis of Methylene-Bridged bis-1,3-Dicarbonyl Compounds, *Org. Lett.*, 2009, **11**(18), 4176–4179.
- 27 À Pericas, A. Shafir and A. Vallribera, Zinc(II) Oxide: An Efficient Catalyst for Selective Transesterification of  $\beta$ -Ketoesters, *Tetrahedron*, 2008, **64**(39), 9258–9263.
- 28 H. M. Meshram, P. N. Reddy, K. Sadashiv and J. S. Yadav, Amberlyst-15®-Promoted Efficient 2-Halogenation of 1,3-Keto-esters and Cyclic Ketones using N-Halosuccinimides, *Tetrahedron Lett.*, 2005, **46**(4), 623–626.
- 29 B. Štefane and S. Polanc, A New Regio- and Chemoselective Approach to  $\beta$ -Keto Amides and  $\beta$ -Enamino Carboxamides via 1,3,2-Dioxaborinanes, *Synlett*, 2004, (04), 698–702.



- 30 N. Micale, R. Ettari, A. Lavecchia, C. Di Giovanni, K. Scarbaci, V. Troiano, S. Grasso, E. Novellino, T. Schirmeister and M. Zappalà, Development of Peptidomimetic Boronates as Proteasome Inhibitors, *Eur. J. Med. Chem.*, 2013, **64**, 23–34.
- 31 R. S. Lodh, A. J. Borah and P. Phukan, Synthesis of Bromohydrins using NBS in Presence of Iodine as Catalyst, *Indian J. Chem.*, 2014, **53B**, 1425–1429.
- 32 M. A. Mercadante, C. B. Kelly, J. M. Bobbitt, L. J. Tilley and N. E. Leadbeater, Synthesis of 4-Acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium Tetrafluoroborate and 4-Acetamido-(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl and their use in Oxidative Reactions, *Nat. Protoc.*, 2013, **8**(4), 666–676.
- 33 C. Prévost, Sur un Complexe Iodo-argento-benzoïque et son Application à l'oxydation des Combinaisons éthyléniques en  $\alpha$ -Glycols, *Comptes Rendus*, 1933, **196**, 1129–1131.
- 34 R. B. Woodward and F. V. Brutcher, cis-Hydroxylation of a Synthetic Steroid Intermediate with Iodine, Silver Acetate and Wet Acetic Acid, *J. Am. Chem. Soc.*, 1958, **80**(1), 209–211.
- 35 C. J. Easton, C. A. Hutton, W. T. Eng and E. R. T. Tiekink, Synthesis of Homochiral Hydroxy- $\alpha$ -amino Acid Derivatives, *Tetrahedron Lett.*, 1990, **31**(48), 7059–7062.
- 36 J. E. Steves and S. S. Stahl, Stable TEMPO and ABNO Catalyst Solutions for User-Friendly (bpy)Cu/Nitroxyl-Catalyzed Aerobic Alcohol Oxidation, *J. Org. Chem.*, 2015, **80**(21), 11184–11188.
- 37 T. L. Suyama, W. H. Gerwick and K. L. McPhail, Survey of Marine Natural Product Structure Revisions: A Synergy of Spectroscopy and Chemical Synthesis, *Bioorg. Med. Chem.*, 2011, **19**(22), 6675–6701.
- 38 N. T. Jacob, J. W. Lockner, V. V. Kravchenko and K. D. Janda, Pharmacophore Reassignment for Induction of the Immunosurveillance Cytokine TRAIL, *Angew. Chem., Int. Ed.*, 2014, **53**(26), 6628–6631.
- 39 J. L. Howard, Y. Sagatov and D. L. Browne, Mechanochemical Electrophilic Fluorination of Liquid Beta-ketoesters, *Tetrahedron*, 2018, **74**(25), 3118–3123.
- 40 A. R. Katritzky and S. Sengupta, Facile Desilylative Hydroxyalkylation and Acylation of 1-Trimethylsilylmethyl-2-pyridone, *Tetrahedron Lett.*, 1987, **28**(45), 5419–5422.
- 41 M. Wittmar, K. Moews and N. Meszaros, *Manufacture of Graft Polyesters*, 2013, DE102012003730.
- 42 S. Iimura, F. Muro, T. Yamasaki and T. Hamada, Preparation of Imidazopyridazine Derivatives having Inhibitory Activity on the Production of TNF- $\alpha$ , WO2009041456, 2009.
- 43 J. Zhang, J. Wang, Z. Qiu and Y. Wang, Highly Regio- and Diastereoselective Halohydroxylation of Plefins: A Facile Synthesis of Vicinal Halohydrins, *Tetrahedron*, 2011, **67**(36), 6859–6867.
- 44 O. Cussó, I. Garcia-Bosch, X. Ribas, J. Lloret-Fillol and M. Costas, Asymmetric Epoxidation with H<sub>2</sub>O<sub>2</sub> by Manipulating the Electronic Properties of Non-heme Iron Catalysts, *J. Am. Chem. Soc.*, 2013, **135**(39), 14871–14878.
- 45 Y. Guindon and J. Rancourt, The Use of Lewis Acids in Radical Chemistry. Chelation-Controlled Radical Reductions of Substituted  $\alpha$ -Bromo- $\beta$ -alkoxy Esters and Chelation-Controlled Radical Addition Reactions, *J. Org. Chem.*, 1998, **63**(19), 6554–6565.
- 46 N. Anand, M. Kapoor, S. Koul, S. C. Taneja, R. L. Sharma and G. N. Qazi, Chemoenzymatic Approach to Optically Active Phenylglycidates: Resolution of Bromo- and Iodohydrins, *Tetrahedron: Asymmetry*, 2004, **15**(19), 3131–3138.
- 47 C. Palomo, J. M. Aizpurua, E. Balentová, A. Jimenez, J. Oyarbide, R. M. Fratila and J. I. Miranda, Synthesis of  $\beta$ -Lactam Scaffolds for Ditopic Peptidomimetics, *Org. Lett.*, 2007, **9**(1), 101–104.