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Direct Access to Highly Functionalized Heterocycles through the Condensation of Cyclic Imines and α -Oxoesters

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Abstract

A facile, gram-scale preparation of 2-hydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-ones and 2-hydroxy-6,7,8,8a-tetrahydroindolizin-3(5*H*)-ones from a condensation cyclization of α -oxoesters with five- and six-membered cyclic imines, respectively, is reported. This transformation enables a concise, three-step synthesis of the natural products phenopyrrozin and *p*-hydroxyphenopyrrozin. Further, biologically relevant scaffolds, such as α -quaternary β -homo prolines and β -lactams, are also prepared in two- to three-steps from the versatile 2-hydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one core.

Graphical Abstract

Owing to a broad prevalence in natural products and pharmaceutical agents, nitrogen-containing heterocycles are highly sought-after motifs. Advances in synthetic methodology to access such scaffolds are directly related to our ability to investigate biological processes and treat human disease.

Isolated in 1995 and 2005 from the marine fungus *Chromocleista* sp., phenopyrrozin¹ and *p*-hydroxyphenopyrrozin² are marine alkaloids containing the 2-hydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one core. Both compounds have been reported to possess moderate antimalarial and antituberculosis activity.³ To date, the only reported synthesis of phenopyrrozin and *p*-hydroxyphenopyrrozin is that of Kothapalli and co-workers, accessing the natural products from proline in 8 and 11 steps, with 4.7% and 5.8% overall yields, respectively (Figure 1a).⁴

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Supporting Information

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¹H, ¹³C, and 2D NMR spectra (PDF)

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Previously, we reported a facile multicomponent reaction, in which in situ generated imines undergo cyclization with α -oxoesters to yield the 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one core.⁵ These reactions are carried out at room temperature in aprotic solvents (Figure 1b). Building upon this work, and expanding our program directed toward the synthesis of nitrogen heterocycles,⁵ we envisioned a concise and general approach to the 2-hydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one and 2-hydroxy-6,7,8,8a-tetrahydroindolizin-3(5*H*)-one scaffolds from the condensation-cyclization of 1-pyrroline and 2,3,4,5-tetrahydropyridine, respectively, with α -oxoesters (Figure 1c).

Surprisingly, under our previously reported conditions, 1-pyrroline does not condense with methyl phenylpyruvate to form phenopyrrozin (**3a**) as expected, but rather undergoes a rapid di-addition to compound **9** (Scheme 1a). Interestingly, **9** is formed as a single diastereomer, and the relative configuration was confirmed by a ¹H-¹H NOSEY experiment. When performed in both polar and nonpolar aprotic solvents, **9** is readily furnished, while only traces of **3a** are observed. In contrast, when the reaction is carried out in polar protic solvents (EtOH, MeOH, MeOH/H₂O), the desired product **3** can be isolated in good yield. It is worth mentioning that polar protic and/or aqueous conditions do not inhibit the rapid formation of **9**, but rather facilitate its conversion to **3**. This surprising reactivity was observed across all substrates, for both five- and six-membered imines.

Although initially unforeseen, this reactivity is supported by the fact that both 1-pyrroline and 2,3,4,5-tetrahydropyridine are known to exist in equilibrium between the monomeric imine and a 1,3,5-triazinane trimer,^{6,7} thus, demonstrating a similar intermolecular head-to-tail interaction between cyclic imines as is observed here (Scheme 1b). Recently, Cui and co-workers reported a similar [2+2+2] addition of 3,4-dihydrocarboline imine to ynones.⁸

In addition to aiding in hydrolysis of **9**, we further attribute the high yields of the 5:1 MeOH/H₂O solvent system (Scheme 2) to the poor solubility of **3** in aqueous methanol, which precipitates as the reaction progresses, thus, driving forward the proposed equilibrium between **9** and **3**. This is supported by the observation that as the reaction progresses in 5:1 MeOH/H₂O, the ratio of **9** to **3** in solution remains relatively constant. As expected, the use of aqueous/organic solvent systems, such as DMF/H₂O and THF/H₂O, in which **3** is soluble, also results in poor conversion. All attempts to disfavor formation of **9** were unsuccessful with the di-addition to **9** prevailing regardless of concentration, order of addition, and stoichiometry.

Similar to our previous work is the rapid rate at which reaction occurs, favoring electron-poor α -oxoesters and electron-rich imines.⁵ We propose such reactivity arises from an initial acid-base reaction between the basic imine and enol moiety of the α -oxoesters, generating an iminium and enolate ion pair, followed by addition of the enolate to the iminium ion, ring closure, and loss of methanol to yield **3**. In the case of cyclic imines, the addition of a second imine occurs before ring closure and condenses with the α -keto moiety of the α -oxoesters to yield **9**.

To explore the substrate scope of this reaction, a variety of heterocycles with the general structure **3** have been prepared from the respective α -oxoesters and cyclic imine (Scheme 2).

1-Pyrroline,⁶ 2,3,4,5-tetrahydropyridine,^{7a,b} and α -oxoesters⁹ were prepared in accordance with literature procedures.

Previous reports note the instability of the 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one moiety to silica gel.^{6,10} As such, we were pleased to find the 5:1 methanol/water solvent system allowed for isolation of products by filtration. To this end, phenopyrrozin (**3a**) and *p*-hydroxyphenopyrrozin (**3b**) were isolated in 69% and 55% yields, respectively (Scheme 2). Both 1-pyrroline and phenylpyruvate ester starting materials are prepared in one step each in quantitative yield or are commercially available; hence, the natural products were synthesized in 3 steps with 69% and 55% overall yields.

1-Pyrroline was then reacted with a variety of electron-rich and electron-poor aromatic pyruvate esters, providing **3c–3g** in high purity and good yields. Our method is also successful for aliphatic-substituted pyruvate esters, providing **3h** and **3i**; however, to prevent depreciation of yields, these derivatives were isolated as their TBS ethers **4h** and **4i**, respectively, before purification by silica gel column chromatography (Scheme 2). The reaction also performs well for six-membered imines, providing **3j–3n** (Scheme 2) in good yields. Unfortunately, unsubstituted product **3o**, arising from methyl pyruvate, was not isolated under our optimized conditions.

We next envisioned leveraging the innate functionality of **3** as a viable platform from which unique, biologically relevant scaffolds may be accessed. One such example is an operationally simple, two- to three-step conversion of **3** to α -quaternary center-containing β -homo prolines (**7**) and bicyclic β -lactams (**8**).

When subjected to standard Tsuji–Trost allylation conditions (Pd-allyl chloride dimer catalyst, rac-BINAP ligand, and base), 2-hydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-ones readily yield the tetrahydro-1*H*-pyrrolizine-2,3-dione scaffold (**5**) (Figure 2).¹¹ For substrates **5a**, **5g**, and **5e**, the reaction proceeded in good yields and 3:1 to 4:1 diastereomeric ratios, and the diastereomers were separable by column chromatography. Alkyl-substituted **3i** did not function as well in this reaction, with **5i** isolated in 20% yield.

Oxidative ring opening of the pyrrolizine-2,3-dione scaffolds was achieved by subjecting **5** to 1 M NaOH in 30% hydrogen peroxide,¹² followed by in situ protection of the resultant amino acid with Boc-anhydride to yield β -homo proline **7**. Boc protection of the nitrogen enabled the amino acids to be purified readily by normal phase column chromatography, where as the nonprotected amino acids proved to be difficult to purify.

The *N*-Boc amino acids (**7a**, **7e**, **7g**) were then able to be converted directly into their corresponding β -lactams in a one-pot, two-step deprotection cyclization (Scheme 3). Treatment of **7** with TFA/DCM (1:1) removed the Boc group, revealing the deprotected amino acid. The β -amino acids were then cyclized with EDC to provide β -lactams **8a**, **8e**, and **8g**.¹³

Additionally, it was found that the in situ generation of the acid chloride of **7a** resulted in intramolecular cyclization to the β -amino acid *N*-carboxyanhydride (NCA) (**10**, Scheme 3). This observation is in agreement with previous literature accounts of the synthesis of NCAs.

¹⁴ Over the past decade, NCAs have gained popularity for their applications in ROP peptide coupling, which has seen utility in the synthesis of biomaterials,¹⁵ functionalized peptides,¹⁶ and pharmaceuticals.¹⁷ This further exemplifies the value of synthetic approaches to functionalized β -amino acids.

In an effort to further expand the scope of the β -lactam synthesis to include spiro-cyclic systems, a similar approach to access β -lactam **8i** was envisioned (Scheme 4); however, poor isolated yields of **3i** after purification by column chromatography, in conjunction with consistently low yields in the Tsuji–Trost allylation of **3i** to **5i**, prompted us to investigate an alternative approach to access dione **5i**. This revised route consisted of protecting the enol moiety of crude **3i** as a vinyl allyl ether, by treatment of **3i** with allyl bromide and K₂CO₃ in acetone. Full conversion was observed in 24 h at room temperature. Interestingly, only O-allylation was observed under these conditions. The vinyl allyl ether then underwent thermal [3 + 3] sigmatropic rearrangement to **5i** upon refluxing in toluene for 24–48 h. With substrate **5i** in hand, we then planned a ring-closing metathesis (RCM) to **6i**, introducing an α -quaternary spiro-cyclic center. Employing the second-generation Grubbs' catalyst in refluxing DCM, **6i** was prepared in 79% yield. As previously described, pyrrolizine-2,3-dione **6i** was converted to β -homo proline **7i** by oxidative ring opening and subsequently **8i** via deprotection and ring closure (Scheme 4).

Given the prevalence of β -lactams in infectious disease related therapeutics, as either β -lactam antibiotics (BLAs) or antibiotic adjuvants, scaffolds such as **8** provide an exciting platform from which unique, α -quaternary center-containing β -lactams may be accessed.

In summary, we have developed a facile method to access 2-hydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-ones and 2-hydroxy-6,7,8,8a-tetrahydroindo-lizin-3(5*H*)-ones from the condensation of α -oxoesters with five- and six-membered cyclic imines. This method provides direct access to the natural products phenopyrrozin and *p*-hydroxyphenopyrrozin in a three-step synthesis. Additionally, the unique reactivity of cyclic imines was explored in the case of compound **9**. Furthermore, we provide a two- to three-step, operationally simple route to biologically relevant β -homo prolines and β -lactams from the 3-hydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one scaffold.

EXPERIMENTAL SECTION

DCM and THF were purified using an alumina filtration system. Reagents were purchased and used as received unless otherwise noted. Reactions were monitored by TLC analysis (precoated silica gel 60 F254 plates, 500 μ m layer thickness), and visualization was accomplished with a 254 nm UV light and by staining with a KMnO₄ solution (1.5 g of KMnO₄, 10 g of K₂CO₃, and 1.25 mL of a 10% NaOH solution in 200 mL of water) and/or staining with I₂ (1 g of I₂, 10 g SiO₂, dry). Reactions were also monitored by HPLC-MS (2.6 μ m C18 50 $\times$ 2.10 mm column). Flash chromatography on SiO₂ was used to purify the crude reaction mixtures and performed on a flash system utilizing prepacked cartridges and linear gradients. Melting points were determined using a capillary melting point apparatus. Chemical shifts were reported in parts per million with the residual solvent peak spectra run at 300, 400, or 700 MHz and are tabulated as follows: chemical shift, multiplicity (s =

singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, bs = broad singlet, dt = doublet of triplet, tt = triplet of triplet), number of protons, and pulse sequence with a d1 of 0 s unless otherwise noted, and are tabulated by observed peak. High-resolution mass spectra were obtained on an ion trap mass spectrometer using heated electrospray ionization (HESI). All cyclic imines,^{6,7a,b} 2-oxoacids,^{9b} and their methyl esters^{9a,c-e} were prepared according to general procedures previously described in literature.

General Procedure for the Synthesis of 2-Hydroxy-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-ones 3a–3g and 2-Hydroxy-6,7,8,8a-tetrahydroindolizin-3(5H)-ones 3j–3n (I)

To a stirred suspension of methyl 2-oxoester (1 equiv) in 5:1 MeOH/H₂O (0.5 M) under inert atmosphere is added dropwise imine (1 equiv) in 5:1 MeOH/H₂O (1.0 M). Stirring is continued at room temperature for 72 h. Upon completion, the product is collected by vacuum filtration and residual solvent is removed in vacuo to yield the title compound.

(RS)-2-Hydroxy-1-phenyl-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one (3a)—

According to general procedure I, methyl-2-hydroxy-3-phenyl acrylate (50 mg, 0.28 mmol) and 1-pyrroline (19 mg, 0.28 mmol) were reacted to yield **3a** (42 mg, 69% yield) as a colorless solid. [65% isolated yield (1.56 g) when run on 11.2 mmol scale]: Mp 177–180°C. R_f = 0.40 (50% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃): δ = 7.74 (dd, J = 7.6, 0.9 Hz, 2H), 7.40 (m, 2H), 7.28 (dd, J = 7.8, 7.1, 1H), 4.53 (dd, J = 10.6, 5.6 Hz, 1H), 3.56 (m, 1H), 3.40 (m, 1H), 2.43 (m, 1H), 2.35 (m, 2H), 1.28 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 171.2, 142.4, 132.4, 128.6, 127.6, 126.8, 124.1, 62.6, 41.8, 30.7, 28.5 HRMS (ESI) m/z calcd for C₁₃H₁₄NO₂ [M + H]⁺ 216.1019, found 216.1018.

(RS)-2-Hydroxy-1-(4-hydroxyphenyl)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one (3b)—

According to general procedure I, methyl-2-hydroxy-3-phenyl acrylate (50 mg, 0.26 mmol) and 1-pyrroline (18 mg, 0.26 mmol) were reacted to yield **3b** (33 mg, 55% yield) as a colorless solid: Mp 214–216 °C. R_f = 0.40 (50% EtOAc/hexanes). ¹H NMR (400 MHz, CD₃OD): δ = 7.63 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 4.48 (dd, J = 10.5, 5.6 Hz, 1H), 3.42–3.36 (m, 1H), 3.33–3.29 (m, 1H), 2.45–2.38 (m, 1H), 2.34–2.27 (m, 2H), 1.18–1.08 (m, 1H). ¹³C NMR (100 MHz, CD₃OD): δ = 173.7, 158.3, 142.0, 129.4, 127.4, 125.7,

116.4, 63.8, 42.9, 32.0, 29.3. HRMS (ESI) m/z calcd for $C_{13}H_{14}NO_3$ $[M + H]^+$ 232.0968, found 232.0964.

(RS)-2-Hydroxy-1-(4-methoxyphenyl)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one (3c)—According to general procedure I, methyl (*Z*)-2-hydroxy-3-(4-

methoxyphenyl)acrylate (53 mg, 0.25 mmol) and 1-pyrroline (18 mg, 0.25 mmol) were reacted to yield **3c** (43 mg, 69% yield) as a colorless solid: Mp 187–189 °C. 1H NMR (400 MHz, $CDCl_3$): δ = 8.67 (b, 1H), 7.72 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 4.46 (dd, J = 10.6, 5.5 Hz, 1H), 3.82 (s, 3H), 3.59–3.49 (m, 1H), 3.36 (ddd, J = 11.3, 8.2, 3.1 Hz, 1H), 2.43–2.22 (m, 3H), 1.33–1.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 159.0, 141.0, 128.2, 125.3, 124.7, 114.0, 62.6, 55.3, 41.8, 30.7, 28.5. HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_3$ $[M + H]^+$ 246.1125, found 246.1124. Trace acetone (<1%) observed in 1H NMR at δ = 2.17 ppm.

(RS)-2-Hydroxy-1-(4-(trifluoromethyl)phenyl)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one (3d)—According to general procedure I, methyl (*Z*)-2-hydroxy-3-(4-(trifluoromethyl)phenyl)acrylate (50 mg, 0.20 mmol) and 1-pyrroline (14 mg, 0.20 mmol) were reacted to yield **3d** (45 mg, 78% yield) as a colorless solid: Mp 178–181 °C. 1H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 4.53 (dd, J = 10.7, 5.5 Hz, 1H), 3.63–3.56 (m, 1H), 3.42 (dd, J = 11.4, 8.6 Hz, 1H), 2.46–2.27 (m, 3H), 1.33–1.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 144.6, 135.9, 129.2, 128.8, 126.7, 125.4, 122.7, 62.4, 41.8, 30.6, 28.4. HRMS (ESI) m/z calcd for $C_{14}H_{13}F_3NO_2$ $[M + H]^+$ 284.0893, found 284.0892. Trace (<1%) 2-oxoester starting material observed in 1H NMR at δ = 3.80 ppm.

(RS)-1-(4-Bromophenyl)-2-hydroxy-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one (3e)

—According to general procedure I, methyl (*Z*)-3-(4-bromophenyl)-2-hydroxyacrylate (50 mg, 0.19 mmol) and 1-pyrroline (13 mg, 0.19 mmol) were reacted to yield **3e** (49 mg, 86% yield) as a colorless solid [86% isolated yield (1.97 g) when run on 7.78 mmol scale]: Mp 216–218 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.61 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 4.53 (dd, J = 10.8, 5.4 Hz, 1H), 3.57–3.52 (m, 1H), 3.40 (dd, J = 11.3, 8.4 Hz, 1H), 2.44–2.28 (m, 3H), 1.32–1.22 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 171.1, 143.1, 131.9, 131.4, 128.3, 123.1, 121.6, 62.6, 41.9, 30.8, 28.7. HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_2\text{Br}$ [$\text{M} + \text{H}$] $^+$ 294.0124, found 294.0120.

(RS)-2-Hydroxy-1-(2-nitrophenyl)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one (3f)

According to general procedure I, methyl (*Z*)-2-hydroxy-3-(2-nitrophenyl)acrylate (mixture of enol and keto tautomer, 50 mg, 0.22 mmol) and 1-pyrroline (18 mg, 0.26 mmol, 1.2 equiv) were reacted to yield **3f** (32 mg, 55% yield) as a pale yellow solid: Mp 207–211 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 7.90 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 4.60 (dd, J = 10.3, 5.5 Hz, 1H), 3.36–3.30 (m, 1H), 3.26–3.22 (m, 1H), 2.28–2.22 (m, 1H), 2.19–2.12 (m, 1H), 2.09–2.03 (m, 1H), 1.21–1.11 (m, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ = 169.0, 148.8, 144.7, 132.6, 129.2, 128.3, 126.4, 124.3, 120.0, 61.9, 41.8, 29.3 27.8. HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_4$ [$\text{M} + \text{H}$] $^+$ 261.0870, found 261.0865.

(RS)-2-Hydroxy-1-(thiophen-2-yl)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one (3g)

According to general procedure I, methyl (*Z*)-2-hydroxy-3-(thiophen-2-yl)acrylate (0.20 g, 1.09 mmol) and 1-pyrroline (90 mg, 1.30 mmol) were reacted to yield **3g** (0.188 g, 78%

yield) as a beige solid. [76% isolated yield (1.41 g) when run on 8.36 mmol scale]: Mp 202–204 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.93 (b, 1H), 7.36 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.31 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.09 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.44 (dd, *J* = 10.6, 5.7 Hz, 1H), 3.59–3.50 (m, 1H), 3.38 (ddd, *J* = 11.3, 8.5, 2.8 Hz, 1H), 2.46–2.20 (m, 3H), 1.39–1.25 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 171.5, 141.2, 135.0, 127.6, 126.3, 125.4, 121.5, 63.1, 42.2, 30.8, 28.6. HRMS (ESI) *m/z* calcd for C₁₁H₁₂NO₂S [M + H]⁺ 222.0583, found 222.0580.

(RS)-2-Hydroxy-1-phenyl-6,7,8,8a-tetrahydroindolizin-3(5H)-one (3j)—According to general procedure I, methyl (*Z*)-2-hydroxy-3-phenyl acrylate (50 mg, 0.28 mmol) and 2,3,4,5-tetrahydropyridine (23 mg, 0.28 mmol) were reacted to yield **3j** (41 mg, 64% yield) as a colorless solid: Mp 191–198 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.68 (d, *J* = 7.3 Hz, 2H), 7.39 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 1H), 4.38 (dd, *J* = 11.7, 3.6 Hz, 1H), 4.19 (dd, *J* = 11.7, 3.6 Hz, 1H), 2.97 (td, *J* = 13.0, 3.6 Hz, 1H), 2.36 (dd, *J* = 13.4, 2.8 Hz, 1H), 1.93 (d, *J* = 13.3 Hz, 1H), 1.81 (d, *J* = 14.5 Hz, 1H), 1.61 (qt, *J* = 13.3, 3.1 Hz, 1H), 1.47–1.35 (m, 1H), 1.06 (qd, *J* = 13.2, 3.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 165.0, 142.5, 131.8, 128.5, 127.2, 127.0, 122.3, 57.1, 40.3, 32.9, 26.2, 23.6. HRMS (ESI) *m/z* calcd for C₁₄H₁₆NO₂ [M + H]⁺ 230.1176, found 230.1172. Trace impurities remaining in ¹H NMR after filtration.

(RS)-2-Hydroxy-1-(thiophen-2-yl)-6,7,8,8a-tetrahydroindolizin-3(5H)-one (3k)—According to general procedure I, methyl (*Z*)-2-hydroxy-3-(thiophen-2-yl)acrylate (50 mg, 0.27 mmol) and 2,3,4,5-tetrahydropyridine (23 mg, 0.27 mmol) were reacted to yield **3k** (52 mg, 81% yield) as a light tan solid: Mp 209–215 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.33 (d, *J* = 5.0 Hz, 1H), 7.29 (d, *J* = 3.6 Hz, 1H), 7.08 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.37 (dd, *J* = 13.2, 3.7 Hz, 1H), 4.09 (dd, *J* = 11.6, 3.7 Hz, 1H), 2.94 (td, *J* = 13.0, 3.6 Hz, 1H), 2.51 (dd, *J* = 13.0, 3.2 Hz, 1H), 1.96 (d, *J* = 14.0 Hz, 1H), 1.82 (d, *J* = 12.7 Hz, 1H), 1.62 (qt, *J* = 13.3, 3.2 Hz, 1H), 1.48–1.36 (m, 1H), 1.23–1.12 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 164.7, 141.1, 134.2, 127.2, 125.3, 124.9, 118.9, 57.6, 40.2, 33.3, 26.2, 23.5. HRMS (ESI) *m/z* calcd for C₁₂H₁₄NO₂S [M + H]⁺ 236.0740, found 36.0736.

(RS)-2-Hydroxy-1-(4-(trifluoromethyl)phenyl)-6,7,8,8a-tetrahydroindolizin-3(5H)-one (3l)—

According to general procedure I, methyl (*Z*)-2-hydroxy-3-(4-(trifluoromethyl)phenyl)acrylate (50 mg, 0.20 mmol) and 2,3,4,5-tetrahydropyridine (17 mg, 0.20 mmol) were reacted to yield **3l** (53 mg, 88% yield) as a colorless solid: Mp 202–205 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.78 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 4.39 (dd, *J* = 13.2, 4.9 Hz, 1H), 4.21 (dd, *J* = 11.7, 3.5 Hz, 1H), 2.99 (td, *J* = 13.0, 3.6 Hz, 1H), 2.37–2.33 (m, 1H), 1.96 (d, *J* = 13.7 Hz, 1H), 1.84 (d, *J* = 13.7 Hz, 1H), 1.63 (q, *J* = 13.3 Hz, 1H), 1.48–1.37 (m, 1H), 1.07 (tdd, *J* = 13.2, 11.7, 3.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 164.6, 144.2, 135.2, 128.9, 127.0, 125.4, 122.8, 120.6, 57.1, 40.4, 32.8, 26.1, 23.5. HRMS (ESI) *m/z* calcd for C₁₅H₁₅F₃NO₂ [M + H]⁺ 236.0740, found 236.0736. Trace impurities remaining in ¹H NMR after filtration

(RS)-2-Hydroxy-1-(4-methoxyphenyl)-6,7,8,8a-tetrahydroindolizin-3(5H)-one (3m)—

According to general procedure I, methyl (*Z*)-2-hydroxy-3-(4-methoxyphenyl)acrylate (50 mg, 0.24 mmol) and 2,3,4,5-tetrahydropyridine (20 mg, 0.24 mmol) were reacted to yield **3m** (28 mg, 45% yield) as a colorless solid: Mp 192–195 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.62 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.14 (dd, *J* = 11.7, 3.6 Hz, 1H), 3.82 (s, 3H), 2.96 (td, *J* = 12.9, 3.5 Hz, 1H), 2.33 (dd, *J* = 13.3, 3.1 Hz, 1H), 1.92 (d, *J* = 13.3 Hz, 1H), 1.80 (d, *J* = 13.1 Hz, 1H), 1.60 (qt, *J* = 13.3, 3.2 Hz, 1H), 1.46–1.34 (m, 1H), 1.05 (qd, *J* = 13.2, 3.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 165.2, 158.7, 140.9, 128.4, 124.5, 122.5, 114.0, 57.1, 55.3, 40.2, 33.1, 26.3, 23.6. HRMS (ESI) *m/z* calcd for C₁₅H₁₈NO₃ [M + H]⁺ 260.1281, found 260.1277.

(RS)-1-(4-Bromophenyl)-2-hydroxy-6,7,8,8a-tetrahydroindolizin-3(5H)-one (3n)

—According to general procedure I, methyl (*Z*)-2-hydroxy-3-(4-bromophenyl)acrylate (28 mg, 0.11 mmol) and 2,3,4,5-tetrahydropyridine (9.0 mg, 0.11 mmol) were reacted to yield **3n** (33 mg, 84% yield) as a light tan solid: Mp 191–196 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.54 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.9 Hz, 2H), 4.37 (dd, J = 13.5, 4.7 Hz, 1H), 4.15 (dd, J = 11.7, 3.6 Hz, 1H), 2.96 (td, J = 13.0, 3.6 Hz, 1H), 2.32 (dd, J = 13.3, 3.1 Hz, 1H), 1.94 (d, J = 13.1 Hz, 1H), 1.82 (d, J = 13.2 Hz, 1H), 1.61 (qt, J = 13.3, 3.2 Hz, 1H), 1.47–1.35 (m, 1H), 1.05 (tdd, J = 13.2, 11.6, 3.4 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 164.7, 142.9, 131.7, 130.6, 128.4, 121.0, 110.0, 57.0, 40.3, 32.9, 26.1, 23.5. HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{15}\text{BrNO}_2$ [$\text{M} + \text{H}$] $^+$ 308.0281, found 308.0278.

General Procedure for the Preparation of TBS Protected Substrates (4h, 4i) (II)

To a stirred solution of methyl 2-oxoester (1.0 equiv) in 5:1 MeOH/ H_2O (0.5 M) under inert atmosphere is added dropwise 1-pyrroline (1.0 equiv) in 5:1 MeOH/ H_2O (1.0 M). Stirring is continued at room temperature for 4 days. The reaction is then diluted with water and extracted with DCM (3 $\times$). The combined organic layers were dried over anhydrous sodium sulfate and filtered, and solvent was removed in vacuo to yield a crude oil. The crude was then redissolved in DCM (0.1 M). To the solution was then added TBSCl (1.2 equiv), followed by triethylamine (2 equiv) and DMAP (0.1 equiv). The reaction was stirred at room temperature for 24 h, while monitored by HPLC-MS. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl and extracted with DCM (3 $\times$). The combined organic layers were then dried over anhydrous sodium sulfate, filtered, and solvent was removed in vacuo. The crude was purified by flash column chromatography (12–100% gradient, EtOAc/hexanes) to yield **4h/4i**.

(RS)-2-((tert-Butyldimethylsilyloxy)-1-pentyl-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one (4h)

—According to general procedure II, methyl 2-oxooctanoate (80 mg, 0.46 mmol) and 1-pyrroline (32 mg, 0.46 mmol, 1 equiv) were reacted to yield **4h** (48 mg, 32% yield) as a colorless oil: ^1H NMR (400 MHz, CDCl_3): δ = 3.94 (dd, J = 10.6, 5.3 Hz, 1H), 3.42–3.35 (m, 1H), 3.27–3.22 (m, 1H), 2.38–2.27 (m, 3H), 2.15–2.04 (m, 2H), 1.51–1.43 (m, 2H), 1.32–1.25 (m, 5H), 0.96 (s, 9H), 0.91–0.87 (m, 3H), 0.27 (s, 3H), 0.22

(s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 172.3, 142.0, 136.3, 63.1, 42.1, 31.9, 30.1, 28.6, 27.7, 25.7, 25.4, 22.4, 18.3, 13.9, -4.03 , -4.36 . HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{34}\text{NO}_2\text{Si}$ $[\text{M} + \text{H}]^+$ 324.2353, found 324.2348.

(RS)-1-Allyl-2-((tert-butyldimethylsilyl)oxy)-5,6,7,7a-tetrahydro-3H-pyrrolizin-3-one (4i)—According to general procedure II, methyl 2-oxohex-5-enoate (62 mg, 0.43 mmol) and 1-pyrroline (20 mg, 0.29 mmol, 1.5 equiv) were reacted to yield **4i** (36 mg, 36% yield) as a colorless oil: R_f = 0.72 (50% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3): δ = 5.82–5.71 (m, 1H), 5.12–5.04 (m, 2H), 3.92 (dd, J = 10.5, 5.5 Hz, 1H), 3.40–3.33 (m, 1H), 3.26–3.21 (m, 1H), 3.12 (dd, J = 15.3, 6.7 Hz, 1H), 3.01 (dd, J = 15.3, 6.7 Hz, 1H), 2.27–2.20 (m, 1H), 2.15–2.04 (m, 2H), 1.05–1.02 (m, 1H), 0.95 (s, 3H), 0.27 (s, 3H), 0.21 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 172.1, 142.4, 134.3, 133.5, 116.9, 63.1, 42.2, 30.3, 30.1, 28.7, 25.8, 18.4, -3.9 , -4.3 . HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{28}\text{NO}_2\text{Si}$ $[\text{M} + \text{H}]^+$ 294.1884, found 294.1878.

General Procedure for the Tsuji–Trost Allylation of **3** to **5** (III)

To a solution of **3** (1 equiv) in degassed toluene (0.05 M) at 0°C was added $t\text{-BuOK}$ (1 equiv). The solution was allowed to stir at 0°C for 15 min. At 0°C , a solution of $[\text{PdCl}(\text{C}_3\text{H}_5)]_2$ (0.05 equiv), rac-BINAP (0.1 equiv), and allyl acetate (2 equiv) in degassed toluene (0.012 M) was added dropwise. The reaction was stirred at 0°C for 1 h, while monitored by LC-MS. Upon completion, solvent was removed in vacuo. ^1H NMR of the crude was used to determine dr. The crude was then purified by flash column chromatography (12–100% gradient, EtOAc/hexanes) to yield **5**.

(±)-1-Allyl-1-phenyltetrahydro-1H-pyrrolizine-2,3-dione (5a)—According to general procedure III, **3a** (50 mg, 0.23 mmol) was reacted to yield **5a** (57 mg, 0.22 mmol, 96% yield, 3:1 dr): (major diastereomer + enantiomer), amorphous solid, ^1H NMR (400 MHz, CDCl_3): δ = 7.32–7.23 (m, 3H), 7.03–7.01 (m, 2H), 5.74–5.63 (m, 1H), 5.21–5.13 (m, 2H), 4.01 (dd, J = 11.3, 5.3 Hz, 1H), 3.72 (dt, J = 12.9, 8.6 Hz, 1H), 3.48 (dt, J = 12.9, 6.3 Hz, 1H), 2.97–2.91 (m, 1H), 2.82 (dd, J = 14.0, 8.3 Hz, 1H), 2.04–1.96 (m, 2H), 1.84–1.77 (m, 1H), 0.90–0.79 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 204.9, 159.2, 138.4, 131.7, 128.8, 127.6, 127.2, 120.8, 64.4, 56.4, 42.6, 41.7, 29.2, 24.2. (minor diastereomer +

enantiomer), amorphous solid, ^1H NMR (400 MHz, CDCl_3): δ = 7.43–7.28 (m, 5H), 5.51 (ddt, J = 17.1, 10.3, 7.0 Hz, 1H), 5.03 (dd, J = 10.3, 1.4 Hz, 1H), 4.96 (dd, J = 17.0, 1.5 Hz, 1H), 4.16 (dd, J = 10.8, 5.4 Hz, 1H), 3.80 (dt, J = 13.2, 8.0 Hz, 1H), 3.57 (ddd, J = 12.7, 9.1, 2.9 Hz, 1H), 2.74 (dd, J = 14.5, 6.9 Hz, 1H), 2.54 (dd, J = 14.5, 7.0 Hz, 1H), 2.34–2.18 (m, 2H), 2.15–2.08 (m, 1H), 2.05–1.91 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 201.5, 158.4, 138.3, 130.9, 128.9, 127.6, 126.9, 120.1, 66.4, 56.2, 42.2, 38.9, 26.3, 24.6. HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 256.1332, found 256.1327.

(±)-1-Allyl-1-(4-bromophenyl)tetrahydro-1H-pyrrolizine-2,3-dione (5e)—

According to general procedure III, **3e** (12 mg, 0.04 mmol) was reacted to yield **5e** (0.13 mg, 0.04 mmol, 99% yield, 3:1 dr): (major diastereomer + enantiomer), amorphous solid, ^1H NMR (400 MHz, CDCl_3): δ = 7.41 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.63 (dddd, J = 16.5, 10.1, 8.1, 6.3 Hz, 1H), 5.18–5.10 (m, 2H), 3.98 (dd, J = 11.3, 5.3 Hz, 1H), 3.75–3.65 (m, 1H), 3.50–3.42 (m, 1H), 2.87 (dd, J = 14.0, 6.3 Hz, 1H), 2.76 (dd, J = 14.0, 8.1 Hz, 1H), 2.05–1.94 (m, 2H), 1.84–1.76 (m, 1H), 0.89–0.74 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 204.2, 158.9, 137.3, 131.9, 131.2, 129.0, 121.8, 121.1, 64.3, 55.8, 42.6, 41.9, 29.4, 24.2. (minor diastereomer + enantiomer), amorphous solid, ^1H NMR (400 MHz, CDCl_3): δ = 7.50 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 5.48 (ddt, J = 17.2, 10.3, 7.0 Hz, 1H), 5.06 (dd, J = 10.2, 1.4 Hz, 1H), 4.95 (dd, J = 17.0, 1.5 Hz, 1H), 4.15–4.10 (m, 1H), 3.83–3.76 (m, 1H), 3.62–3.54 (m, 1H), 2.68 (dd, J = 14.5, 7.1 Hz, 1H), 2.51 (dd, J = 14.5, 6.9 Hz, 1H), 2.31–2.18 (m, 2H), 2.05–1.94 (m, 1H), 1.28–1.23 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 201.2, 158.0, 137.4, 131.8, 130.5, 128.8, 121.6, 120.4, 65.8, 55.8, 42.2, 38.9, 26.2, 24.6. HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{Br}$ $[\text{M} + \text{H}]^+$ 334.0437, found 334.0433.

(±)-1-Allyl-1-(thiophen-2-yl)tetrahydro-1H-pyrrolizine-2,3-dione (5g)—According to general procedure III, **3g** (0.50 g, 2.2 mmol) was reacted to yield **5g** (0.50 g, 1.9 mmol, 86% yield, 4.3 dr): (major diastereomer + enantiomer), amorphous solid, ^1H NMR (400 MHz, CDCl_3): δ = 7.17 (d, J = 5.18 Hz, 1H), 6.85 (dd, J = 5.13, 3.64 Hz, 1H), 6.56 (d, J = 3.63 Hz, 1H), 5.72–5.62 (m, 1H), 5.18–5.10 (m, 2H), 3.97 (dd, J = 10.6, 5.4 Hz, 1H), 3.66

(dt, J = 13.0, 8.7 Hz, 1H), 3.43 (dt, J = 12.9, 6.4 Hz, 1H), 2.92–2.86 (m, 1H), 2.77 (dd, J = 13.8, 8.4 Hz, 1H), 2.01–1.95 (m, 2H), 1.85–1.80 (m, 1H), 1.10–0.99 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 201.6, 158.6, 140.6, 131.5, 126.8, 125.6, 125.0, 121.0, 64.0, 54.8, 42.7, 41.3, 27.8, 24.2. (minor diastereomer + enantiomer), amorphous solid, ^1H NMR (400 MHz, CDCl_3): δ = 7.28 (dd, J = 5.1, 1.2 Hz, 1H), 7.10 (dd, J = 3.6, 1.2 Hz, 1H), 7.01 (dd, J = 5.1, 3.6 Hz, 1H), 5.56 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 5.08 (dd, J = 10.3, 1.6 Hz, 1H), 5.01 (dd, J = 17.0, 1.5 Hz, 1H), 4.22 (dd, J = 10.9, 5.5 Hz, 1H), 3.84–3.76 (m, 1H), 3.62–3.56 (m, 1H), 2.67 (dd, J = 14.4, 7.0 Hz, 1H), 2.58 (dd, J = 14.4, 6.9 Hz, 1H), 2.31–2.22 (m, 2H), 1.98–1.88 (m, 1H), 1.32–1.25 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 199.9, 158.0, 140.6, 130.7, 127.0, 125.5, 125.1, 120.4, 66.6, 54.6, 42.4, 40.2, 26.0, 24.5. HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 262.0896, found 262.0894.

(RS)-1,1-Diallyltetrahydro-1H-pyrrolizine-2,3-dione (5i)—Crude compound **3i** (assuming 100% conversion, 1 equiv) was dissolved in acetone (0.1 M), under inert atmosphere, and cooled to 0 °C. Potassium carbonate (1.4 equiv) was then added in one portion, followed by allyl bromide (2.8 equiv). The reaction was then warmed to room temperature, and stirring was continued for 24 h. Upon completion, the suspension was filtered, and solvent was removed in vacuo to yield the crude as a brown oil, which was dissolved in toluene (0.1 M) and refluxed for 24 h. Reaction progress was monitored by TLC. Upon completion, the reaction was cooled to room temperature, and solvent was removed in vacuo. The crude was then purified by flash column chromatography (12–100% gradient, EtOAc/hexanes) to yield **5i** (0.28 g, 20% yield over 3 steps) as a colorless crystalline solid. Mp 79–82 °C. R_f = 0.15 (50% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3): δ = 5.69–5.62 (m, 2H), 5.17–5.07 (m, 4H), 3.80 (dd, J = 11.1, 5.5 Hz, 1H), 3.75–3.68 (m, 1H), 3.53–3.47 (m, 1H), 2.46 (dd, J = 14.1, 8.1 Hz, 1H), 2.37 (dd, J = 14.2, 6.8 Hz, 1H), 2.30 (dd, J = 14.3, 7.8 Hz, 1H), 2.23–2.18 (m, 2H), 2.14–2.06 (m, 1H), 2.05–1.97 (m, 1H), 1.75–1.64 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 204.4, 158.7, 131.9, 130.9, 120.3, 120.1, 63.3, 51.8, 42.0, 37.7, 36.2, 26.3, 24.7. HRMS (ESI) m/z calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_2$ [$\text{M} + \text{H}$] $^+$ 220.1332, found 220.1328.

(RS)-5',6',7',7a'-Tetrahydrospiro[cyclopentane-1,1'-pyrrolizin]-3-ene-2',3'-dione (6i)—To a solution **5i** (0.28 g, 1.3 mmol, 1 equiv) in anhydrous DCM (25 mL, 0.05 M) was added Grubbs' catalyst second generation (53 mg, 0.063 mmol, 0.05 equiv). The solution

was refluxed for 10 min. Upon cooling to room temperature, solvent was removed in vacuo. The crude was purified by flash column chromatography (12–100% gradient, EtOAc/hexanes) to yield **6i** (0.20 g, 84% yield) as a colorless crystalline solid. Mp 77–79 °C. ¹H NMR (400 MHz, CDCl₃): δ = 5.65 (dt, *J* = 5.7, 2.2 Hz, 1H), 5.55 (dt, *J* = 5.6, 2.1, 1H), 3.74–3.64 (m, 2H), 3.38 (ddd, *J* = 12.6, 8.4, 4.1 Hz, 1H), 2.92–2.83 (m, 1H), 2.50–2.26 (m, 3H), 2.11–1.94 (m, 3H), 1.55–1.41 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 204.8, 159.4, 129.0, 127.2, 66.8, 55.4, 42.4, 41.9, 39.0, 27.2, 24.6. HRMS (ESI) *m/z* calcd for C₁₁H₁₄NO₂ [M + H]⁺ 192.1019, found 192.1017.

General Procedure for the Oxidative Opening/Protection of **5/6i** to **7 (IV)**.⁷

To a suspension of **5** (or **6i**) in aqueous NaOH (1 M, 4 equiv) at 0 °C was dropwise added H₂O₂ (30% in H₂O, 4 equiv). The reaction was warmed to room temperature, and stirring was continued for 18–36 h. Upon complete conversion to the β-amino acid, the reaction was cooled to 0 °C, and NaHCO₃ (1 equiv) followed by Boc₂O (1.5 equiv) in THF (0.3 M) were added. The reaction was then warmed to room temperature and stirred for 1 h. Upon completion, the pH was raised to ~6 using saturated aqueous citric acid. The reaction mixture was then extracted with DCM (3×). The combined organic layers were then dried over Na₂SO₄ and filtered, and solvent was removed in vacuo. The crude was then purified by flash column chromatography (12–75% gradient, EtOAc/hexanes) to yield **7**.

(±)-2-(1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)-2-phenylpent-4-enoic acid (**7a**)—

According to general procedure IV, **5a** (92 mg, 0.36 mmol) was reacted to yield **7a** (63 mg, 50% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.37–7.24 (m, 5H), 5.81–5.67 (m, 1H), 5.09–4.99 (m, 2H), 4.73 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.60–3.49 (m, 1H), 2.92 (d, *J* = 7.0 Hz, 2H), 2.65–2.48 (m, 1H), 2.04–1.83 (m, 2H), 1.47 (s, 9H), 1.31–1.23 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): 178.5, 156.9, 138.3, 134.0, 130.3, 129.2, 128.6, 127.8, 127.1, 118.49, 80.9, 63.6, 60.1, 48.1, 40.8, 28.5, 28.2, 23.8. HRMS (ESI) *m/z* calcd for C₂₀H₂₈NO₄ [M + H]⁺ 346.2013, found 346.2009. Trace, inseparable impurities in ¹H NMR.

(±)-2-(4-Bromophenyl)-2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)pent-4-enoic acid (**7e**)—

According to general procedure IV, **5e** (48 mg, 0.14 mmol) was reacted to yield **7e** (25 mg, 41% yield) as a colorless oil. (12–75) ¹H NMR (400 MHz, CDCl₃): δ = 7.42 (d,

$J = 8.7$ Hz, 2H), 7.25 (d, $J = 8.8$ Hz, 2H), 5.68 (ddt, $J = 17.0, 10.0, 7.1$ Hz, 1H), 5.08–4.99 (m, 2H), 4.70 (dd, $J = 8.5, 4.9$ Hz, 1H), 3.58–3.46 (m, 1H), 2.92–2.79 (m, 2H), 2.62–2.47 (m, 1H), 2.04–1.95 (m, 1H), 1.84–1.76 (m, 1H), 1.45 (s, 3H), 1.32–1.25 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 177.5, 156.5, 136.8, 133.3, 131.1, 130.7, 121.2, 118.7, 80.8, 63.4, 59.3, 48.0, 40.1, 28.4, 28.2, 23.7$. HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_4\text{Br}$ $[\text{M} + \text{H}]^+$ 424.1118, found 424.1110.

(±)-2-(1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)-2-(thiophen-2-yl)-pent-4-enoic acid (7g)—According to general procedure IV, **5g** (51 mg, 0.20 mmol) was reacted to yield **7g** (24 mg, 35% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.27$ (d, $J = 5.1$ Hz, 1H), 7.10 (d, $J = 3.6$ Hz, 1H), 6.97 (dd, $J = 5.1, 3.7$ Hz, 1H), 5.66 (ddt, $J = 17.0, 10.0, 6.8$ Hz, 1H), 5.09 (d, $J = 17.0$ Hz, 1H), 4.99 (d, $J = 10.3$ Hz, 1H), 4.61–4.58 (m, 1H), 3.53–3.37 (m, 1H), 3.00 (dd, $J = 14.3, 7.1$ Hz, 1H), 2.86 (dd, $J = 14.0, 6.3$ Hz, 2H), 1.95–1.91 (m, 2H), 1.47 (s, 9H), 1.36–1.20 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 177.3, 155.9, 140.6, 133.6, 127.1, 125.7, 125.6, 118.5, 80.2, 65.6, 57.8, 40.1, 41.7, 28.4, 27.5, 23.4$. HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_4\text{S}$ $[\text{M} + \text{H}]^+$ 352.1577, found 352.1570.

(RS)-1-(1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)cyclopent-3-ene-1-carboxylic acid (7i)—According to general procedure IV, **6i** (51 mg, 0.27 mmol) was reacted to yield **7i** (58 mg, 77% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): $\delta = 5.62$ –5.58 (m, 2H), 4.37 (d, $J = 7.4$ Hz, 1H), 3.65–3.55 (m, 1H), 3.28–3.21 (m, 1H), 2.85–2.77 (m, 2H), 2.52 (dd, $J = 16.5, 8.8$ Hz, 2H), 2.02–1.93 (m, 1H), 1.85–1.73 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 182.6, 155.8, 129.1, 128.7, 79.8, 61.9, 58.8, 48.1, 39.5, 38.9, 28.4, 28.3, 23.7$. HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{24}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 282.1700, found 282.1694.

General Procedure for Cyclization of **7** to **8** (V).8

Compound **7** (1 equiv) was dissolved in DCM/TFA (1:1, 0.075 M) at 0 °C. The reaction was stirred at 0 °C for 20 min while monitored by LC-MS. Upon completion of removal of the Boc group, volatiles were removed in vacuo. The crude was then redissolved in MeCN (0.015 M), followed by the addition of triethylamine (3 equiv) and EDCI (2.2 equiv). The solution was then refluxed for 1 h, until all starting material was consumed. Upon completion, the reaction was cooled to room temperature, and solvent was removed in vacuo. The crude was purified by flash column chromatography (12–75% gradient, EtOAc/hexanes) to yield **8**.

(±)-6-Allyl-6-phenyl-1-azabicyclo[3.2.0]heptan-7-one (8a)—According to general procedure V, **7i** was reacted to yield **8i** as a colorless oil (58% isolated yield). ^1H NMR (400 MHz, CDCl_3): δ = 7.38–7.29 (m, 4H), 7.26–7.20 (m, 1H), 5.88–5.74 (m, 1H), 5.11–5.08 (m, 1H), 5.08–5.04 (m, 1H), 3.74 (dd, J = 8.5, 5.4 Hz, 1H), 3.48 (dt, J = 10.9, 7.7 Hz, 1H), 2.98–2.91 (m, 1H), 2.76 (dt, J = 7.4, 1.4 Hz, 2H), 1.99–1.85 (m, 3H), 1.16–1.01 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 179.8, 138.7, 133.4, 128.5, 127.2, 126.9, 118.6, 63.2, 62.3, 45.0, 44.6, 29.7, 28.9. HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{18}\text{NO}$ $[\text{M} + \text{H}]^+$ 228.1383, found 228.1379.

(±)-6-Allyl-6-(4-bromophenyl)-1-azabicyclo[3.2.0]heptan-7-one (8e)—According to general procedure V, **7e** was reacted to yield **8e** as a colorless oil (53% isolated yield). ^1H NMR (400 MHz, CDCl_3): δ = 7.44 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 5.77 (ddt, J = 17.4, 118.9, 7.3 Hz, 1H), 5.09–5.03 (m, 2H), 3.72 (dd, J = 8.5, 5.5 Hz, 1H), 3.46 (dt, J = 11.1, 7.9 Hz, 1H), 2.94 (ddd, J = 11.3, 7.6, 4.3 Hz, 1H), 2.72 (d, J = 7.3 Hz, 2H), 1.99–1.85 (m, 3H), 1.09–0.99 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 179.2, 137.7, 132.9, 131.7, 129.0, 121.0, 118.9, 62.7, 62.2, 45.0, 44.5, 29.6, 28.8. HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{17}\text{NOBr}$ $[\text{M} + \text{H}]^+$ 306.0488, found 306.0485.

(±)-6-Allyl-6-(thiophen-2-yl)-1-azabicyclo[3.2.0]heptan-7-one (8g)—According to general procedure V, **7g** was reacted to yield **8g** as a colorless oil (45% isolated yield). ^1H NMR (400 MHz, CDCl_3): δ = 7.24 (dd, J = 5.1, 1.2 Hz, 1H), 7.01 (dd, J = 3.5, 1.2 Hz, 1H), 6.95 (dd, J = 5.1, 3.5 Hz, 1H), 5.86 (ddt, J = 14.4, 10.1, 7.2 Hz, 1H), 5.17–5.10 (m, 2H), 3.71 (dd, J = 7.7, 6.2 Hz, 1H), 3.55 (dt, J = 11.1, 7.6 Hz, 1H), 2.95–2.89 (m, 1H), 2.86–2.79 (m, 2H), 1.99–1.91 (m, 2H), 1.84–1.77 (m, 1H), 1.22–1.14 (m, 1H). ^{13}C NMR (100 MHz,

CDCl₃): δ = 178.4, 140.5, 133.1, 126.8, 125.9, 124.9, 118.9, 63.1, 60.8, 45.4, 44.0, 29.7, 27.4. HRMS (ESI) m/z calcd for C₁₃H₁₅NOS [M + H]⁺ 234.0947, found 234.0944.

(RS)-1-Azaspiro[bicyclo[3.2.0]heptane-6,1'-cyclopentan]-3'-en-7-one (8i)—

According to general procedure V, **7i** was reacted to yield **8i** as an amorphous solid (43% isolated yield). ¹H NMR (400 MHz, CDCl₃): δ = 5.64 (dt, J = 7.8, 5.7 Hz, 2H), 3.53–3.46 (m, 2H), 2.98 (dq, J = 17.1, 1.8 Hz, 1H), 2.84 (ddd, J = 11.6, 7.5, 4.4 Hz, 1H), 2.67 (dt, J = 17.3, 12.0 Hz, 1H), 2.60 (dt, J = 17.1, 2.0 Hz, 1H), 2.09–1.93 (m, 3H), 1.54–1.44 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 183.9, 128.8, 128.6, 65.7, 59.0, 45.1, 42.0, 36.2, 29.6, 24.1. HRMS (ESI) m/z calcd for C₁₀H₁₄NO [M + H]⁺ 164.1070, found 164.1068.

(±)-Methyl 6-phenyl-1,2,3,6a,7,8,9,10a-octahydrodipyrrolo[1,2a:1',2'-c]pyrimidine-5-carboxylate (9)—

To a solution of methyl 1-2-hydroxy-3-phenyl acrylate (125 mg, 0.70 mmol, 1 equiv) in DCM (3.5 mL, 0.2 M) was added 1-pyrroline (97 mg, 1.4 mmol, 2 equiv). The reaction was stirred at room temperature for 3 h, while monitored by HPLC-MS. Upon completion, solvent was removed in vacuo, and the crude was purified by flash column chromatography (12–75% gradient, EtOAc/hexanes) to yield **9** (83 mg, 38% yield) as a lime-green oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.27 (dd, J = 7.6, 7.6 Hz, 2H), 7.20 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 8.1 Hz, 2H), 4.38 (t, J = 6.4 Hz, 1H), 3.84 (t, J = 6.0 Hz, 1H), 3.46 (s, 3H), 3.28–3.32 (m, 2H), 2.95 (td, J = 8.9, 4.8 Hz, 1H), 2.62 (q, J = 8.2 Hz, 1H), 2.17–2.13 (m, 1H), 1.99–1.96 (m, 1H), 1.94–1.90 (m, 2H), 1.89–1.86 (m, 1H), 1.83–1.79 (m, 2H), 1.59–1.56 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.2, 139.0, 134.4, 128.6, 127.9, 126.4, 119.4, 75.5, 64.1, 51.6, 48.8, 45.2, 29.5, 28.1, 23.1, 22.4. HRMS (ESI) m/z calcd for C₁₈H₂₃N₂O₂ [M + H]⁺ 299.1754, found 299.1748.

(±)-4-Allyl-4-phenyltetrahydro-1H-pyrrolo[1,2-c][1,3]oxazine-1,3(4H)-dione (10)

—To a solution of **7a** (21 mg, 0.06 mmol, 1 equiv) in DCM (1.2 mL, 0.05 M) at 0 °C were added DMF (0.5 µL, 0.1 equiv) and diisopropylethylamine (26 µL, 2.5 equiv), followed by oxalyl chloride (10 µL, 2 equiv). The solution was stirred at 0 °C for 5 h, while monitored by HPLC-MS. Upon completion, the reaction was slowly quenched with water and extracted with DCM (3×). The combined organic layers were dried over anhydrous Na₂SO₄ and filtered, and solvent was removed in vacuo to yield a crude oil. The oil was then purified by flash column chromatography (12–75% gradient, EtOAc/hexanes) to yield **10** (10 mg, 75% yield) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.42–7.31 (m, 3H), 7.19 (dd, *J* = 8.1, 1.6 Hz, 2H), 5.88 (dddd, *J* = 17.0, 10.0, 8.8, 5.2 Hz, 1H), 5.29–5.21 (m, 2H), 4.05 (dd, *J* = 8.3, 6.7 Hz, 1H), 3.56 (ddd, *J* = 11.1, 7.9, 3.0 Hz, 1H), 3.17–3.09 (m, 2H), 2.78 (dd, *J* = 14.1, 8.9 Hz, 1H), 2.06–1.98 (m, 1H), 1.84–1.74 (m, 1H), 1.69–1.55 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 168.6, 147.1, 134.6, 132.6, 129.1, 128.5, 127.3, 120.5, 58.9, 53.2, 46.7, 38.7, 26.1, 23.1. HRMS (ESI) *m/z* calcd for C₁₆H₁₈NO₃ [M + H]⁺ 272.1281, found 272.1275.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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a) Previous work: **b) Our previous work:** **c) This work:** **Figure 1.**

(a) Previous synthesis of phenopyrrozin and *p*-hydroxyphenopyrrozin. (b) Our previous investigations into the reactivity of in situ generated imines toward α -oxoacid chlorides and α -oxoesters. (c) This work.

Figure 2.
Tsuji-Trost allylation of **3**.

Scheme 1.

(a) Unexpected Reactivity of 1-Pyrroline with Methyl Phenylpyruvate to **9** under Aprotic Conditions and to Phenopyrrozin (**3a**) in 5:1 MeOH/H₂O and (b) Equilibrium between Monomeric Imine and Trimer

Scheme 2. Substrate Scope of α -Oxoester and Cyclic Imine Condensation to Scaffold 3

Scheme 3. Conversion of 5 to β -Homo Prolines (7) and Bicyclic β -Lactams (8)

Scheme 4.
Revised Approach to Compounds 7i and 8i