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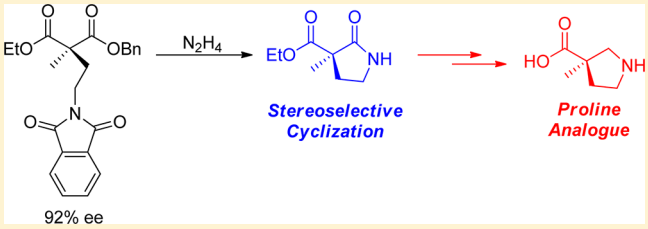
A Stereoselective Cyclization Strategy for the Preparation of γ-Lactams and Their Use in the Synthesis of α-Methyl-β-Proline

Souvik Banerjee, Justin Smith, Jillian Smith, Caleb Faulkner, and Douglas S. Masterson*

Department of Chemistry and Biochemistry, The University of Southern Mississippi, 118 College Drive No. 5043, Hattiesburg, Mississippi 39406, United States

Supporting Information

ABSTRACT: A straightforward stereoselective and enantiodivergent cyclization strategy for the construction of γ-lactams is described. The cyclization strategy makes use of chiral malonic esters prepared from enantiomerically enriched monoesters of disubstituted malonic acid. The cyclization occurs with the selective displacement of a substituted benzyl alcohol as the leaving group. A Hammett study illustrates that the cyclization is under electronic control. The resulting γ-lactam can be readily converted into a novel proline analogue.



Lactams are an important class of amides. Lactams are frequently found in a number of biologically important molecules and are useful synthetic intermediates in the preparation of various materials.[1,2] Several synthetic methods have been reported for the preparation of γ-lactams from readily available precursors.[3] For example, γ-lactams have been prepared utilizing aza-Michael additions,[4,5] reduction of nitro compounds followed by cyclization,[6] reduction of γ-azido esters followed by cyclization,[7] ring expansion of β-lactams,[8] cycloadditions,[9] and the imino-Mukaiyama−Aldol reaction.[10] Several methods have also been explored that allow for the enantioselective formation of γ-lactams utilizing chiral auxiliaries,[3,6] enatiomerically enriched starting materials,[11,12] and organocatalysts.[5,11] Herein, we report on our efforts to prepare γ-lactams utilizing an enantioselective cyclization strategy and conversion of the γ-lactam product into an unnatural proline analogue. The described strategy makes use of the widely reported enantioselective hydrolysis of prochiral malonate esters by pig liver esterase (PLE)[13−20] followed by a novel cyclization providing the γ-lactam products.[21]

We had cause to prepare compound **4** from **3** in our attempt to determine the absolute stereochemistry of **3** by synthetic means (Scheme 1). Upon treatment of **4** with hydrazine a cyclization took place resulting in compounds **5** and **6** as illustrated in Scheme 1. Interestingly, the **5**/**6** ratio was 10:1 as determined by ^{1}H NMR resulting in a selective cyclization that favored ring closure by attack at the benzyl ester over the ethyl ester. The cyclization selectivity results in an enantioselective cyclization strategy as **5** has the *R*-absolute stereochemistry and **6** has the *S*-absolute stereochemistry.

The ability to control the cyclization reaction utilizing such a straightforward set of synthetic manipulations could prove useful in the enantioselective preparation of γ-lactams from simple half-ester starting materials such as **3**. The 10:1 selectivity was interesting given that both esters are relatively open toward nucleophilic attack by the amine nucleophile. In an attempt to better understand the factors controlling the selectivity of the cyclization we performed a series of cyclization experiments where substituents were introduced on the para position of the aromatic ring of the benzyl ester (Scheme 2).

The introduction of substituents on the para position allow for a Hammett plot to be constructed providing insight into the electronic factors controlling the selectivity of the cyclization. We hypothesized that the σ_p constants[22] would provide insight into the electronic activation of the benzyl ester toward nucleophilic attack. Figure 1 illustrates the results of the Hammett analysis with a strong correlation of product ratio to σ_p.

The positive slope clearly indicates that electron-withdrawing substituents favor cyclization to γ-lactam **5** over γ-lactam **6**. This illustrates that benzyl esters with para electron-withdrawing substituents activate the carbonyl toward nucleophilic attack by the primary amine resulting in selective formation of **5**.

We wanted to further develop the stereoselective cyclization concept to provide **6** as the major product. Being able to provide **6** as the major product would allow for a potentially useful enantiodivergent cyclization strategy. The results of the Hammett study suggest that it would be difficult to obtain high selectivity in the formation of **6** by exploiting electronic factors on the benzyl ester alone. We prepared diester **7** from **3** that would introduce steric hindrance (Scheme 3). The ethyl ester should serve as the better electrophile from a steric congestion point of view resulting in stereoselective cyclization to **8**. Product **8** is an analogue of **6** and has the same absolute stereochemistry as **6**.

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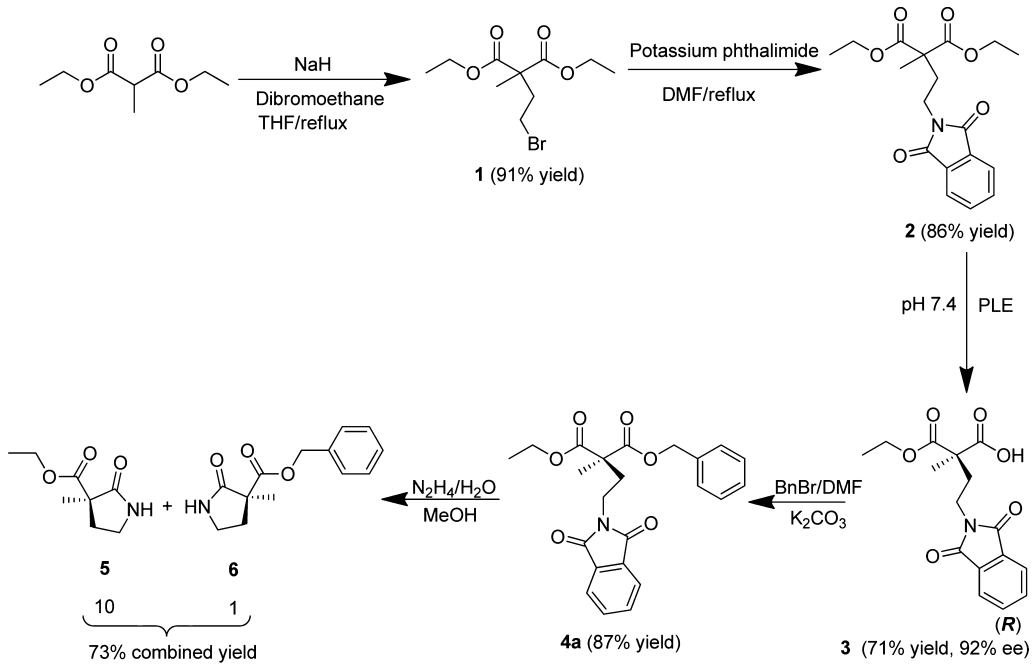
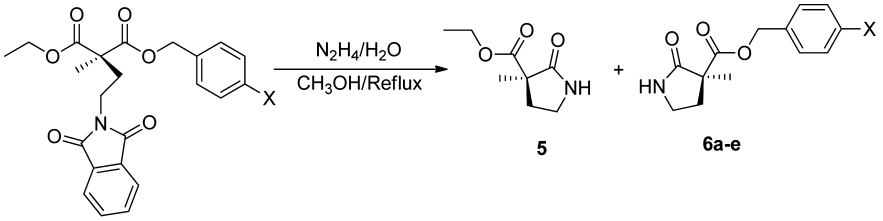
Scheme 1. Preparation of γ-Lactams (PLE = Crude Pig Liver Esterase)



Scheme 2. Cyclization Using Various Benzyl Esters



From ***3***

4a, X = H
4b, X = F
4c, X = CH_3
4d, X = NO_2
4e, X = CF_3

Ratio (combined % yield)

5/6a: 10/1 (73%)
5/6b: 9.1/1 (83%)
5/6c: 6.5/1 (92%)
5/6d: 78/1 (79%)
5/6e: 32/1 (84%)

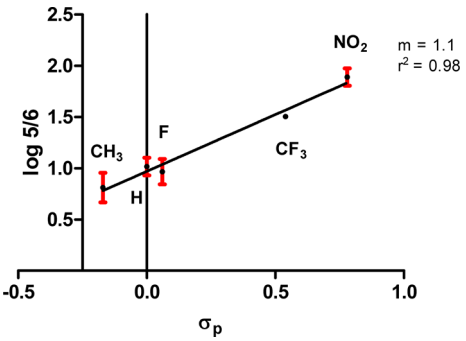


Figure 1. Hammett plot.

The results illustrated in Scheme 3 demonstrate that stereoselective formation of **8** occurs in a 9:1 ratio providing a route to the (*S*)-γ-lactam from **3**.

We wanted to demonstrate the potential utility of the γ-lactams prepared above as precursors to unnatural amino acids. Upon inspection of **5** it is conceivable that a β-proline analogue[23−29] could be readily prepared by reduction of the lactam to a secondary amine. We attempted a direct reduction of the lactam with various reducing agents and conditions known to reduce lactams to amines.[12,30] However, all attempts at direct reduction of the lactam resulted in reduction of both the ester and lactam functional groups providing a complex mixture of products. The synthetic approach shown in Scheme 4 was used to overcome the over-reduction problem and ultimately provide the unprotected β-proline analogue in reasonable overall yield.

Compound **5** was treated with NaH and benzyl bromide to provide the mixture **9a**/**9b** in good yield (68%). We suspect that the formation of **9b** was due to the presence of benzyl alcohol in our commercially obtained benzyl bromide leading to partial transesterification. ^{1}H NMR analysis of the commercial benzyl bromide indicated a significant quantity of benzyl alcohol. However, obtaining a mixture of **9a**/**9b** was of no real significance as the ester would eventually be transformed into the free acid and the mixture was carried on through the subsequent steps. The mixture of **9a**/**9b** was converted in 80% yield to thiolactam **10a**/**10b** using Lawesson reagent.[11] The thiolactam mixture was then easily reduced to the primary amines **11a**/**11b** by hydrogenation over Raney nickel catalyst in good yield.[31−33] Interestingly, we were able to

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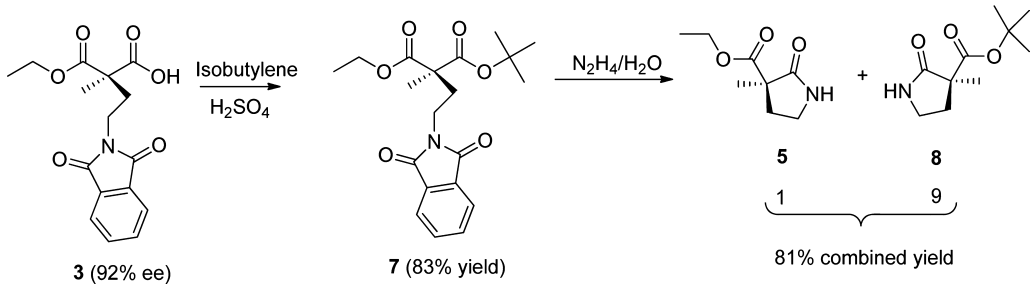
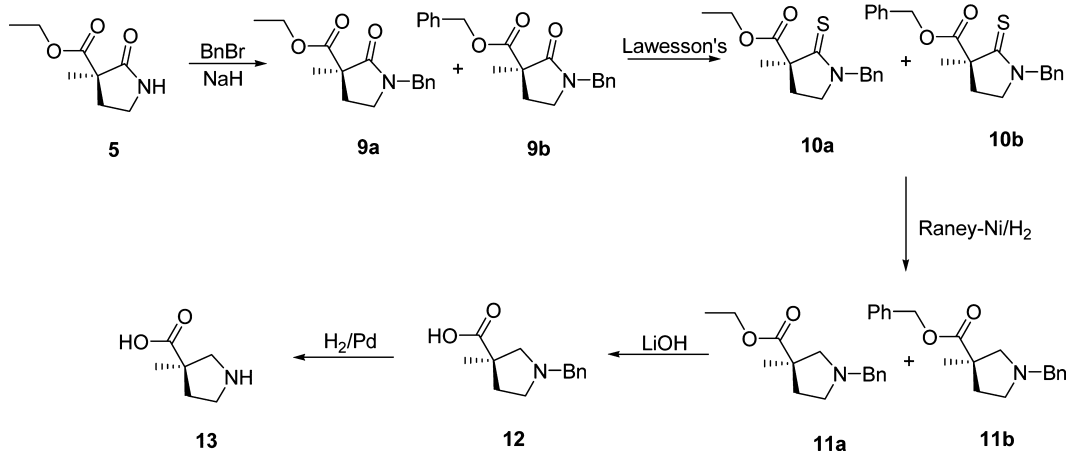
Scheme 3. Selective Cyclization Providing (*S*)-γ-Lactam 8



Scheme 4. Conversion of 5 into Proline Analogue 13



isolate **11a** by radial chromatography and obtain good analytical data on **11a** (see the Supporting Information). The **11a**/**11b** mixture was then subjected to saponification giving **12** in 78% yield. Amino acid **12** was then converted to the α-methyl-β-proline analogue **13** in 91% yield by hydrogenation over Pd/C catalyst. The overall yield of **13** from **5** is 28% over the five straightforward steps shown in Scheme 4.

We have shown that enantioselective γ-lactam formation is possible from **4** with judicious choice of benzyl ester. The highest level of selectivity was observed using **4d** containing a para nitro substituent on the benzyl ester. The cyclization selectivity has a strong correlation to σ_p as demonstrated in the Hammett analysis. The positive slope of the Hammett plot indicates that electron withdrawing substituents in the para position of the benzyl ester activate the benzyl ester carbonyl toward electrophilic attack. We have demonstrated that γ-lactam **5** can be readily converted into **13** providing straightforward access to a new class of proline analogue.

EXPERIMENTAL SECTION

General Methods. THF, CH_2Cl_2, and DMF were dried by passage through activated alumina. All reagents were used as received unless otherwise stated. Melting points were obtained in open capillary tubes and are uncorrected. Flash chromatography was performed using P-60 silica gel, and TLC analysis was performed using silica precoated TLC plates. Radial chromatography was performed on normal-phase precoated silica rotors. HRMS was obtained using ESI/FTICR-MS, and low-resolution MS were obtained by ESI/ion trap. Pig liver esterase (PLE) refers to the commercially available crude preparation.

Synthesis of Diethyl 2-(2-Bromoethyl)-2-methylmalonate (1). A volume of 100 mL of dry THF was added to 2.5 g of NaH (63 mmol, 60% suspension in mineral oil) under a N_2 atmosphere. The THF solution was cooled to 0 °C. A 50 mL solution of 10 g of diethyl-2-methylmalonate (57 mmol) in THF was added over 30 min, with stirring. The reaction mixture was allowed to stir for 60 min at rt. The generated enolate was dripped into a 100 mL solution of 21.4 g of dibromoethane (114 mmol) in THF over 60 min with stirring under N_2 atmosphere. The reacton mixture was then heated to reflux in solvent for 12 h. The solution was cooled to rt, diluted with ether (300 mL), washed twice with 1 N HCl, washed with brine, dried over $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure. The resulting pale yellow liquid was distilled to remove the excess dibromoethane giving 14.6 g (52 mmol, 91%) of **1** as a colorless liquid. IR (cm^{-1}): 2982, 1726. ^1H NMR ($CDCl_3$, 400 MHz): 4.20 (q, 4H, J = 7 Hz), 3.39 (t, 2H, J = 7 Hz), 2.44 (t, 2H, J = 7 Hz), 1.44 (s, 3H), 1.26 (t, 6H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 171.0, 61.0, 54.0, 39.0, 27.0, 29.0, 14.0. ESI-MS $[C_{10}H_{18}BrO_4]^+$: 281, 283. HRMS $[C_{10}H_{17}BrO_4Na]^+$: calcd 303.0202, found 303.0201.

Synthesis of Diethyl 2-Methyl-2-[2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (2). A 100 mL solution of 6 g of **1** (21 mmol) in DMF was placed in a 250 mL sealed tube. A 4.6 g (25 mmol) portion of potassium phthalimide was added to the sealed tube. The reaction mixture was stirred at 90 °C overnight. The reaction mixture was cooled to rt, diluted with 300 mL of H_2O, and extracted with Et_2O (3 × 200 mL). The combined organic layer was washed with water (10 × 100 mL), washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure giving the crude product as a white solid. The crude was recrystallized from cold Et_2O giving 6.2 g (18 mmol, 86%) of **2** was a white solid: R_f = 0.48 (30% EtOAc/hexanes). IR (cm^{-1}): 3000, 1773, 1721, 1709. Mp = 68 °C. ^1H NMR ($CDCl_3$, 400 MHz): 7.84 (m, 2H), 7.71 (m, 2H), 4.18 (q, 4H, J = 7 Hz), 3.74 (m, 2H), 2.25 (m, 2H), 1.54 (s, 3H), 1.27 (t, 6H, J = 7 Hz). ^{13}C- NMR ($CDCl_3$, 75 MHz): 171.7, 168.0, 134.0, 132.0, 123.4, 62.0, 52.5, 34.0, 33.9, 20.0, 14.0. HRMS $[C_{18}H_{21}NO_6Na^+]$: calcd 370.1261, found 370.1257.

Synthesis of (*R*)-2-(*N*-Ethylphthalimido)-3-ethoxy-2-methyl-3-oxopropanoic Acid (3). A 10 g portion of **2** (29 mmol) was dispersed in 1000 mL of rapidly stirring phosphate buffer (0.1 N, pH 7.4). A 97 mg portion of pig liver esterase (PLE) (27 units/mg, 90 units per mmol of the substrate) was added to the buffer. The pH was

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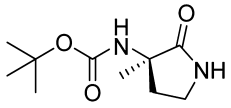
maintained at 7.4 with an auto buret set to deliver 1 equiv of 1 N NaOH solution. The hydrolysis proceeded for 2 days. The reaction mixture was acidified with 12 M HCl to pH 1 and extracted three times with 600 mL of Et_2O. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure giving crude product as colorless viscous oil. The crude product was purified by flash chromatography (40% EtOAc/hexanes) giving 7.2 g (22.5 mmol, 71%) of **3** as a white solid. The % ee was determined to be 92% by chiral HPLC (Chiralcel OJ-H, 305 nm, 5% Ipr-OH/hexane) $t_{R(S)}$ = 52.93 min (area = 307.51), $t_{R(R)}$ = 55.56 min (area = 7596.17). R_f = 0.35 (40:60 EtOAc/hexanes). $[\alpha]^{24}_D$ = +9.7 (c = 1, MeOH). Mp = 83 °C. IR (cm^{-1}): 3100 (broad), 2923, 1751, 1684, 1608. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.38 (bs, 1H), 7.84 (m, 2H), 7.73 (m, 2H), 4.21 (q, 2H, J = 7 Hz), 3.77 (t, 2H, J = 8 Hz), 2.28 (m, 2H), 1.56 (s, 3H), 1.30 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): 175.0, 173.0, 169.0, 135.0, 133.0, 24.0, 62.0, 53.0, 35.0, 34.6, 20.0, 14.0. HRMS [$C_{16}H_{17}NO_6Na^+$]: calcd 342.0948, found 342.0945. The stereochemistry of **3** was determined to be (*R*) by conversion to the known **14** and comparison of the optical rotation. Compound **5** was saponified using 1 N NaOH/EtOH at reflux over 1 h to provide the carboxylic acid that was subjected to a Curtius rearrangement to obtain the free amine that was subsequently treated with $(BOC)_2O$ providing the target compound **14**. $[\alpha]^{24}_D$ = −16 (c = 0.35, $CHCl_3$)].[34]



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General Procedure for the Synthesis of 4a−e. A 250 mL round-bottom flask was charged with 9.9 g of **3** (31 mmol), 4.3 g of K_2CO_3 (31 mmol), 100 mL of anhydrous DMF, and a stirbar. A solution of the appropriately substituted benzyl bromide (28 mmol) in 20 mL of anhydrous DMF was slowly added over 15 min. The reaction was allowed to stir approximately 12 h under a nitrogen atmosphere. The reaction mixture was then diluted with 100 mL of water, and the resulting mixture was washed with Et_2O (3 × 100 mL). The combined ether layer was washed with water (5 × 100 mL) and brine (2 × 100 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was isolated by flash chromatography (40% Et_2O/hexanes).

Synthesis of (*S*)-1-Benzyl-3-ethyl-2-methyl-[2-(1,3-dioxoisoindolin-2-yl)ethyl]malonate (4a). Compound **4a** was synthesized following the general synthetic procedure for the preparation of **4a−e**. An 11 g portion of product (27 mmol, 87%) was obtained after flash chromatography purification as a colorless liquid. R_f = 0.2 (40% Et_2O/hexanes). $[\alpha]^{24}_D$ = −3.08 (c = 1, $CHCl_3$). IR (cm^{-1}): 2980, 1773, 1708. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.83 (m, 2H), 7.70 (m, 2H), 7.33 (m, 5H), 5.15 (m, 2H), 4.10 (m, 2H), 3.74 (m, 2H), 2.28 (m, 2H), 1.56 (s, 3H), 1.16 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 171.4, 171.3, 168.0, 135.5, 134.0, 132.0, 128.5, 128.3, 128.1, 123.0, 67.0, 61.0, 52.0, 33.8, 33.8, 20.0, 14.0. HRMS [$C_{23}H_{23}NO_6Na^+$]: calcd 432.1417, found 432.1406.

Synthesis of (*S*)-1-(4-Fluorobenzyl)-3-ethyl-2-methyl-[2-(1,3-dioxoisoindolin-2-yl)ethyl]malonate (4b). Compound **4b** was synthesized following the general synthetic procedure for the preparation of **4a−e**. A 9.95 g portion of product (23.3 mmol, 75%) was obtained after purification as a colorless liquid. R_f = 0.25 (40% Et_2O/hexanes). $[\alpha]^{24}_D$ = −3.7 (c = 1, $CHCl_3$). IR (cm^{-1}): 2984, 1773, 1708. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.83 (m, 2H), 7.71 (m, 2H), 7.33 (m, 2H), 7.03 (m, 2H), 5.11 (m, 2H), 4.10 (m, 2H), 3.72 (m, 2H), 2.26 (m, 2H), 1.55 (s, 3H), 1.16 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 171.4, 171.3, 163.0 (d, ^1J = 250 Hz), 134.0, 132.0, 131.0 (d, ^4J = 3.6 Hz), 130.0 (d, ^3J = 8.5 Hz), 123.0, 115.0 (d, ^2J = 22 Hz), 123.0, 66.0, 62.0, 52.0, 33.8, 33.7, 20.0, 14.0. HRMS [$C_{23}H_{22}FNO_6Na^+$]: calcd 450.1323, found 450.1312.

Synthesis of (*S*)-1-(4-Methylbenzyl)-3-ethyl-2-methyl-[2-(1,3-dioxoisoindolin-2yl)ethyl]malonate (4c). Compound **4c** was synthesized following the general synthetic procedure for the preparation of **4a−e**. A 9.4 g portion of product (22.3 mmol, 72%) was obtained after purification as colorless liquid. R_f = 0.24 (40% Et_2O/hexanes). $[\alpha]^{24}_D$ = −5.3 (c = 1, $CHCl_3$). IR (cm^{-1}): 2983, 1773, 1708. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.83 (m, 2H), 7.70 (m, 2H), 7.22 (d, 2H, J = 8 Hz), 7.14 (d, 2H, J = 8 Hz), 5.11 (m, 2H), 4.10 (m, 2H), 3.73 (m, 2H), 2.34 (s, 3H), 2.26 (m, 2H), 1.55 (s, 3H), 1.16 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 171.4, 171.3, 168.0, 138.0, 134.0, 132.5, 132.0, 129.0, 128.0, 123.0, 67.0, 62.0, 52.0, 34.0, 21.0, 20.0, 14.0. HRMS [$C_{24}H_{25}NO_6Na^+$]: calcd 446.1574, found 446.1565.

Synthesis of (*S*)-1-(4-Nitrobenzyl)-3-ethyl-2-methyl-[2-(1,3-dioxoisoindolin-2yl)ethyl]malonate (4d). Compound **4d** was synthesized following the general synthetic procedure for the preparation of **4a−e**. A 10.27 g portion of product (22.6 mmol, 73%) was obtained after purification as a white solid. Mp = 65 °C. R_f = 0.1 (40% Et_2O/hexanes). $[\alpha]^{24}_D$ = +1.4 (c = 1, $CHCl_3$). IR (cm^{-1}): 2983, 1773, 1729, 1707, 1517. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.23 (d, 2H, J = 8 Hz), 7.83 (m, 2H), 7.72 (m, 2H), 7.52 (d, 2H, J = 8 Hz), 5.25 (m, 2H), 4.16 (m, 2H), 3.74 (m, 2H), 2.29 (m, 2H), 1.59 (s, 3H), 1.21 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 171.2, 171.1, 168.0, 148.0, 143.0, 134.0, 132.0, 128.0, 124.0, 123.0, 66.0, 62.0, 52.0, 34.0, 33.8, 20, 14. HRMS [$C_{23}H_{22}N_2O_8Na^+$]: calcd 477.1268, found 477.1266.

Synthesis of (*S*)-1-(4-Trifluoromethylbenzyl)-3-ethyl-2-methyl-[2-(1,3-dioxoisoindolin-2yl)ethyl]malonate (4e). Compound **4e** was synthesized following the general synthetic procedure for the preparation of **4a−e**. A10.8 g portion of product (22.6 mmol, 87%) was obtained after purification as a colorless liquid. R_f = 0.26 (40% Et_2O/hexanes). $[\alpha]^{24}_D$ = −8.33 (c = 3, $CHCl_3$). IR (cm^{-1}): 2983, 1773, 1709. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.83 (m, 2H), 7.71 (m, 2H), 7.62 (d, 2H, J = 8 Hz), 7.46 (d, 2H, J = 8 Hz), 5.20 (s, 2H), 4.12 (m, 2H), 3.73 (m, 2H), 2.29 (m, 2H), 1.57 (s, 3H), 1.17 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 171.3, 171.2, 168.0, 139.0, 134.0, 132.0, 130.0 (q, J = 33 Hz), 128.0, 125.0 (q, J = 4 Hz), 123.0, 122.0, 66.0, 62.0, 52.0, 34.0, 33.8, 20.0, 14.0. HRMS [$C_{24}H_{22}F_3NO_6Na^+$] calcd 500.1291, found 500.1278.

Synthesis of (*R*)-Ethyl 3-Methyl-2-oxopyrrolidine-3-carboxylate (5). A volume of 930 μL (10.2 mmol) 35% hydrazine in water was added to a solution of 3.8 g (9.3 mmol) of **4a** in 50 mL of MeOH. The mixture was heated to reflux solvent overnight. A white precipitate was observed within 1 h of reflux. The reaction mixture was allowed to cool to rt, and the resulting mixture was filtered. The filtrate was evaporated under reduced pressure. The resulting residue was taken up in CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography using 30% hexanes/EtOAc giving 1.2 g of a 10:1 mixture of **5**:**6** as a white solid. The mixture was further recrystallized in cold Et_2O giving 1 g (6 mmol, 64.5%) of pure **5** as white crystals. R_f (**5**) = 0.31 (30% hexanes/EtOAc). Mp = 63 °C. $[\alpha]^{23}_D$ = +19.0 (c = 2, MeOH). IR (cm^{-1}): 3245, 2985, 1726, 1698, 1660. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.06 (bs, 1H), 4.20 (m, 2H), 3.47 (m, 1H), 3.36 (m, 1H), 2.64 (m, 1H), 2.02 (m, 1H), 1.45 (s, 3H), 1.28 (t, 3H, J = 7 Hz), ^{13}C NMR ($CDCl_3$, 100 MHz): 177.0, 172.0, 61.0, 51.0, 40.0, 34.0, 20.0, 14.0. HRMS [$C_8H_{13}NO_3Na^+$]: calcd 194.0788, found 194.0795.

Synthesis of (*S*)-1-*tert*-Butyl-3-ethyl-2-methyl-[2-(1,3-dioxoisoindolin-2yl)ethyl]malonate (7). A volume of 600 μL of concd H_2SO_4 was added to a solution of 2 g of **3** (6 mmol) in 30 mL CH_2Cl_2 in a 100 mL sealed tube. The solution was cooled to −7 °C. A volume of 6 mL condensed isobutylene was added to the solution. The tube was sealed tightly and allowed to stir overnight at rt. The tube was uncapped and allowed to stir for 2 h at ambient pressure to allow excess isobutylene to evaporate. The solution was diluted with 30 mL of CH_2Cl_2 and gently washed three times with 1 N NaOH (50 mL). The CH_2Cl_2 layer was dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed (40% EtOAc/hexanes) giving 1.8 g (5 mmol, 83%) of **7** as colorless viscous liquid. The viscosity of the material made removal of residual solvent impractical, and **7** was utilized in the subsequent reaction without further purification. R_f = 0.51 (40% EtOAc/hexanes). IR (cm^{-1}): 2979, 1774, 1709. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.84 (m, 2H), 7.71 (m, 2H), 4.17 (m, 2H), 3.72 (m, 2H), 2.19 (m, 2H), 1.50 (s, 3H), 1.48 (s, 9H), 1.28 (t, 3H, J = 7

Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 172.0, 170.5, 168.0, 134.0, 132.2, 123.3, 82.0, 61.0, 53.0, 34.0, 33.8, 28.0, 20.0, 14.0. HRMS [$C_{20}H_{25}NO_6Na^+$]: calcd 398.1574, found 398.1568.

Synthesis of (*S*)-*tert*-Butyl 3-Methyl-2-oxopyrrolidine-3-carboxylate (8). A volume of 398 μL (4.4 mmol) of 35% hydrazine in water was added to a solution of 1.5 g (4 mmol) **7** in 25 mL MeOH. The mixture was heated to reflux solvent overnight. A white precipitate was observed within 1 h of reflux. The reaction mixture was allowed to cool to rt and the solution was filtered. The filtrate was evaporated under reduced pressure and taken up in CH_2Cl_2. The resulting mixture was washed with water, and the organic layer was dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed using 30% hexanes/EtOAc giving 0.62 g of a 9:1 mixture of **8**:**5** as a white solid. The mixture was further recrystallized in cold Et_2O giving 0.52 g (2.6 mmol, 65%) pure **8** as a white solid: R_f (**8**) = 0.27 (30% hexanes/EtOAc). Mp = 130 °C. IR (cm^{-1}): 3255, 2970, 1727, 1688, 1660. $[\alpha]_D^{23}$ = −14.3 (*c* = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): 6.44 (bs, 1H), 3.45 (m, 1H), 3.33 (m, 1H), 2.55 (m, 1H), 2.0 (m, 1H), 1.46 (s, 9H), 1.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 177.0, 171.0, 81.0, 51.0, 40.0, 34.0, 28.0, 20.0. HRMS [$C_{10}H_{17}NO_3Na^+$]: calcd 222.1101, found 222.1097.

Synthesis of (*R*)-Ethyl 1-Benzyl-3-methyl-2-oxopyrrolidine-3-carboxylate (9a/9b). A solution of 3.6 g (22 mmol) of **5** in 20 mL of anhydrous THF was added slowly to a suspension of 0.62 g NaH (26 mmol) in 10 mL of THF at 0 °C under a N_2 atmosphere. The reaction mixture was allowed to stir for 5 min. A volume of 3.3 mL (4.75 g, 24 mmol) of BnBr was added dropwise to the reaction mixture at 0 °C. The reaction mixture was allowed to stir for 10 min at 0 °C and then allowed to warm to rt. The reaction was continued for 1 h at rt. A volume of 15 mL of dry DMF was added to the reaction mixture, which continued to stir for 2 h. The reaction mixture was poured into 25 mL of H_2O. The water layer was extracted with Et_2O (3 × 50 mL). The combined ether layer was washed with water (5 × 30 mL), dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed (gradient, 15−20% EtOAc/hexanes) giving 3.8 g (15 mmol, 68%) of a 4:1 (as determined by NMR) inseparable mixture of **9a** and **9b** as a colorless oil. The mixture was utilized in the next step without further purification. R_f = 0.27 (20% EtOAc/hexanes). IR (cm^{-1}): 2979, 1735, 1685. ^{1}H NMR ($CDCl_3$, 400 MHz) (**9a**/**9b** mixture): 7.29 (m, 7.5H), 5.16 (m, 0.5H), 4.6 (m, 1.25H), 4.36 (m, 1.27H), 4.17 (m, 2H), 3.33 (m, 1.26H), 3.17 (m, 1.25H), 2.46 (m, 1.25H), 1.89 (m, 1.27H), 1.50 (s, 0.76H), 1.47 (s, 3H), 1.23 (t, 3H, *J* = 7 Hz). ESI-MS [$C_{15}H_{20}NO_3$, **9a**]$^+$: calcd 261.3, found 262.2. ESI-MS [$C_{20}H_{22}NO_3$, **9b**]$^+$: calcd 324.6, found 324.1.

Synthesis of (*S*)-Ethyl 1-Benzyl-3-methyl-2-thioxopyrolidine-3-carboxylate (10a/10b). A 5.3 g (13 mmol) portion of Lawesson's reagent was added to a solution of 3.8 g (15 mmol) of **9a**/**9b** mixture in 20 mL of anhydrous toluene under a N_2 atmosphere. The reaction mixture was heated to 95 °C and stirred overnight. The toluene layer was evaporated under reduced pressure and the residue was chromatographed (20% EtOAc/hexanes) giving 3.3 g (12 mmol, 80%) of a 4:1 mixture (as determined by NMR) of **10a**:**10b** as a colorless oil. The conversion of lactam (**9a**) to the corresponding thiolactam (**10a**) was confirmed by comparing the ^{13}C NMR chemical shift of the lactam (**9a**) carbonyl carbon (172 ppm) to the thiolactam (**10a**) carbonyl carbon (202 ppm). The mixture of **10a**/**10b** was utilized in the next step without further purification. R_f = 0.35 (20% EtOAc/hexanes). IR (cm^{-1}): 2980, 1733, 1505, 1449. ^{1}H NMR ($CDCl_3$, 400 MHz) (**10a**/**10b** mixture): 7.29 (m, 7.3H), 5.18 (m, 2H), 4.82 (m, 1.23H), 4.16 (q, 2H, *J* = 7 Hz), 3.70 (m, 1.24H), 3.51 (m, 1.25H), 2.51(m, 1.23H), 1.92 (m, 1.32H), 1.61 (s, 0.68H), 1.58 (s, 3H), 1.21 (t, 3H, *J* = 7 Hz). ESI-MS [$C_{15}H_{20}NO_2S$, **10a**]$^+$: calcd 277.4, found 278.1. ESI-MS [$C_{20}H_{22}NO_2S$, **10b**]$^+$: calcd 340.1, found 340.2.

Synthesis of (*R*)-Ethyl 1-Benzyl-3-methylpyrrolidine-3-carboxylate (11a). A 0.5 g portion of **10a**/**10b** was dissolved in 15 mL of 4:1 THF/EtOH. A 0.05 g portion of Raney-Ni slurry in water (10% by weight) was added to the solution. The solution was stirred vigorously under a H_2 atmosphere for 4 h, at which point the reaction was found to be complete by TLC. The mixture was filtered through a Celite bed, and the filtrate was evaporated under reduced pressure. The product was purified by radial chromatography using 20% hexanes/CH_2Cl_2 to give 0.25 g (1.01 mmol, 72%) of **11a** as a colorless liquid: R_f = 0.32 (20% hexanes/CH_2Cl_2). IR (cm^{-1}): 2974, 2790, 1725, 1452. $[\alpha]^{24}_D$ = −8 (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) (**11a**): 7.3 (m, 5H), 4.13 (q, 2H, *J* = 7 Hz), 3.61 (m, 2H), 2.94 (d, 1H, *J* = 9 Hz), 2.64 (m, 2H), 2.41 (m, 2H), 1.65 (m, 1H), 1.33 (s, 3H), 1.25 (t, 3H, *J* = 7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) (**11a**): 177.0, 139.0, 128.5, 128.2, 127.0, 64.0, 61.0, 60.0, 54.0, 48.0, 36.0, 25.0, 14.0. HRMS [$C_{15}H_{21}NO_2Na^+$]: calcd 270.1464, found 270.1463.

Synthesis of (*R*)-1-Benzyl-3-methylpyrrolidine-3-carboxylic Acid (12). A 0.13 g portion of LiOH (6 mmol) was added to a solution of 0.46 g (2 mmol) of **11a** in 12 mL of 3:2 H_2O/EtOH. The reaction was stirred at rt for 24 h and determined to be complete by TLC. The mixture was acidified to pH 3 (4 N HCl), and the water layer was evaporated under reduced pressure giving a colorless gummy residue. The gummy residue was triturated with MeOH multiple times, and the MeOH fractions were dried over $MgSO_4$. The solvent was removed under reduced pressure giving 0.34 g (1.56 mmol, 78%) of **12** as a colorless liquid: R_f = 0.13 (5% MeOH/CH_2Cl_2). IR (cm^{-1}): 3371(broad), 2946, 2615, 1712, 1455. $[\alpha]_D^{23}$ = −11.3 (*c* = 1, MeOH). ^{1}H NMR (CD_3OD, 400 MHz): 7.58 (m, 2H), 7.50 (m, 3H), 4.44 (m, 2H), 3.87 (d, 1H, *J* = 12 Hz), 3.51 (m, 2H), 3.21 (d, 1H, *J* = 12 Hz), 2.58 (m, 1H), 2.09 (m, 1H), 1.47 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 176.0, 130.4, 130.2, 129.7, 129.0, 61.0, 58.0, 53.0, 35.0, 22.0. HRMS [$C_{13}H_{17}NO_2Na^+$]: calcd 242.1151, found 242.1145.

Synthesis of (*R*)-3-Methylpyrrolidine-3-carboxylic Acid (13). A 0.3 g (2.3 mmol) portion of **12** was dissolved in 15 mL of MeOH and added to 0.03 g of Pd/C (10% by weight). The solution was allowed to stir overnight under a H_2 atmosphere at rt. The resulting mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure giving 0.27 g (2.1 mmol, 91%) of **13** as a white solid. Mp = 98 °C. IR (cm^{-1}): 3392 (broad), 3177, 2877, 1704. $[\alpha]^{24}_D$ = −20.4 (*c* = 0.33, MeOH). ^{1}H NMR (CD_3OD, 400 MHz): 3.78 (m, 1H), 3.48 (m, 1H), 3.38 (m, 1H), 3.10 (d, 1H, *J* = 12 Hz), 2.49 (m, 1H), 2.01 (m, 1H), 1.45 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 176.0, 53.0, 48.5, 45.0, 35.0, 21.0. HRMS [$(C_6H_{11}NO_2)_2Na^+$]: calcd 281.1472, found 281.1468.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra of all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: douglas.masterson@usm.edu.

Notes

The authors declare no competing financial interest.

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