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An enantiodivergent synthesis of C^{α}-methyl-nipecotic acid analogues from δ-lactam derivatives obtained through a highly stereoselective cyclization strategy

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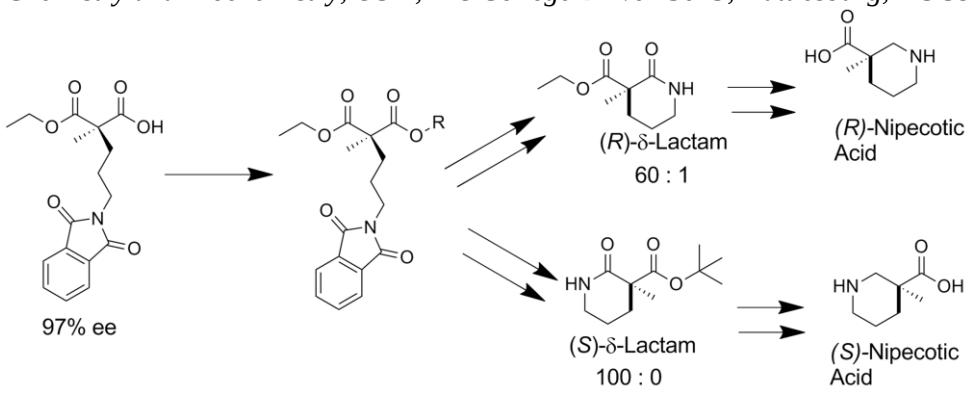

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An enantiodivergent synthesis of C^{α}-methyl nipecotic acid analogues from δ-lactam derivatives obtained through a highly stereoselective cyclization strategy

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ABSTRACT

A stereoselective and enantiodivergent strategy for the construction of δ-lactams is described. The strategy utilizes chiral malonic esters prepared from enantiomerically enriched mono esters of disubstituted malonic acid. A cyclization occurs with the selective displacement of a substituted benzyl alcohol as the leaving group. The resulting δ-lactams are then converted into nipecotic acid analogues using straightforward transformations. The resulting nipecotic acid analogues proved capable organocatalysts in Mannich reactions.

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1. Introduction

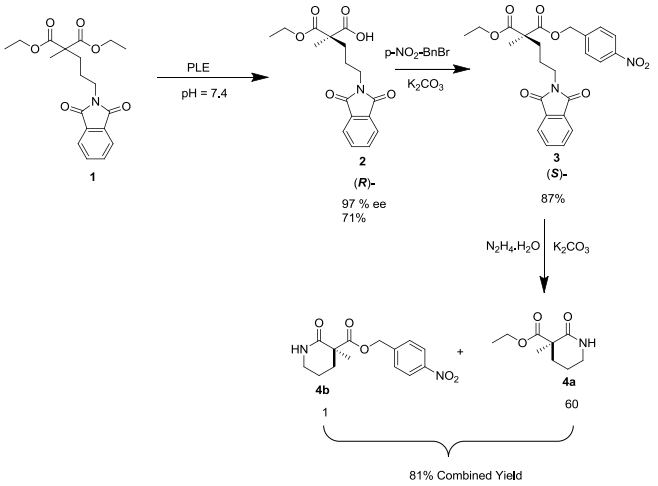
δ-Lactams constitute an important class of compounds in synthetic chemistry and biology. They are often found in important building blocks of a variety of biologically intriguing natural products and as key intermediates in many potent bioactive compounds.[1-4] In addition, δ-lactams are useful precursors to piperidine analogues that are essential pharmacophores in a number of medicinal compounds currently on the market or in advanced clinical studies.[3, 5-8] One of the most important classes of the piperidine family is the piperidine-3-carboxylic acids, otherwise known as derivatives of nipecotic acid. These nipecotic acid analogues are important structural motifs in several natural and synthetic bioactive molecules.[1, 6-10] Hence, it is important to have a concise and efficient synthetic strategy to prepare δ-lactams in order to construct a variety of nipecotic acid analogues.

Recently a number of synthetic strategies have been established to prepare δ-lactams. Some of these strategies include N-heterocyclic catalyzed intramolecular amidations,[11] palladium catalyzed intramolecular amidations,[12] aza-Diels-Alder reactions,[13] intramolecular lactone-amine coupling,[4] gold catalyzed intramolecular C-C couplings of β-ketoamide to unactivated alkenes,[14] and palladium catalyzed intramolecular hydroamidations of alkynes.[15] There have also been several methods detailing the enantioselective synthesis of δ-lactams through ring closing metathesis reactions of enantiomerically pure precursors,[16] nitrilase catalyzed ring expansion of aziridines,[17] and the use of organophosphorus reagents as organocatalysts.[18] Unlike δ-lactams, there are few reports detailing the asymmetric synthesis of nipecotic acid analogues; many of these strategies rely on functional group modifications of preformed nicotinic acids or nipecotic acid derivatives.[9, 10, 19, 20] However, the asymmetric synthesis of piperidine derivatives utilizing a stereoselective cyclization approach is surprisingly rare. To the best of our knowledge, Shintani *et al.* is the first to report a synthesis of diastereomerically enriched nipecotic acid analogues through a palladium catalyzed decarboxylative cyclization.[9] Therefore, there is a need for additional straightforward methods capable of preparing enantiomerically enriched nipecotic acid derivatives.

We have recently demonstrated that γ-lactams can be readily prepared by a stereoselective cyclization strategy.[21] These corresponding γ-lactams were then readily converted into highly optically enriched β-proline derivatives.[21] Hence, we wanted to employ this cyclization strategy to prepare δ-lactams in a stereoselective manner.

2. Results and Discussion

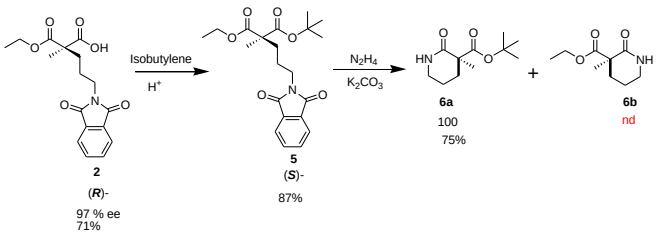
Recently, we have reported a Pig Liver Esterase (PLE) catalyzed asymmetric hydrolysis of the prochiral malonic ester **1**.[22] This biocatalytic hydrolysis of **1** resulted in chiral malonic acid-ester **2** with high enantiomeric purity (97% ee), and good yields (71%) as shown in the Scheme 1. The enantiomerically enriched malonic acid-ester **2** was determined to be predominantly the (*R*)-enantiomer by synthetic means. The acid ester **2** was then converted into benzyl ester **3**. In our previous study, we witnessed that the *para*-NO_2-benzyl ester readily undergoes stereoselective cyclization upon removal of the phthalimide protecting group. Upon treatment of **3** with hydrazine hydrate, a cyclization took place resulting in δ-lactams **4a**, and **4b** as shown in Scheme 1. The ratio of **4a**:**4b** was 60:1 as determined by ^{1}H-NMR. Therefore, the results show a high propensity towards cyclization along with a high selectivity to form δ-lactam **4a**.



Scheme 1. Synthesis of δ-lactams

The strategy illustrated in Scheme 1 shows a straightforward approach whereby the manipulation of this type of ester allows for a high level of cyclization control. This demonstrates a simple strategy that can be very useful in the construction of δ-lactams and their derivatives.

We decided to further explore this cyclization strategy to obtain **4b** as the major product. The ability to construct **4b** as the major product would provide access to a useful enantiodivergent strategy to prepare δ-lactams. However, in our previous study a Hammet study demonstrated the difficulties in acquiring **4b** as the major product simply by exploiting the electronic factors through substituted benzyl esters. In order to address this issue, we synthesized diester **5** from **2** to introduce steric congestion as shown in Scheme 2.

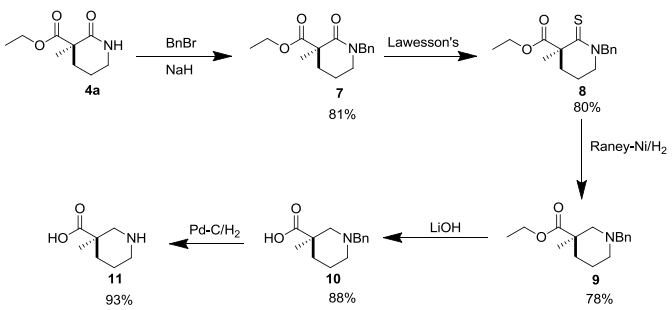


Scheme 2. Selective cyclization proving access to (*S*)-δ-lactam

From a steric congestion standpoint, the ethyl ester in **5** should be more accessible towards nucleophilic attack by the free amine. Upon treatment with hydrazine, **6a** was obtained as the only product and there was no indication of the formation of **6b** as indicated by ^{1}H-NMR. **6a** is a derivative of **4b** with the same absolute stereochemistry as **4b**. Therefore, introduction of steric hindrance gives rise to a highly stereoselective, and potentially stereospecific, cyclization strategy to prepare (*S*)-δ-lactams. To the best of our knowledge, this is the first time an enantiodivergent strategy has been optimized to prepare such δ-lactams.

Over the last few years, C^{α}-methyl-nipecotic acid has served as an important structural entity in a number of synthetic and natural therapeutic lead compounds. For example, a group of scientists from Merck have discovered a potent NK_1 receptor antagonist, where (*R*)-C^{α}-methyl-nipecotic acid is used as an essential building block.[7] Nisho *et al.* have come up with dipeptidyl peptidase IV inhibitors consisting of (*R*)-C^{α}-Methyl-nipecotic acid derivative serving as pharmacophore.[5, 6] Despite a number of practical applications, asymmetric synthesis of C^{α}-methyl-nipecotic acid have been rarely reported in recent years. We wanted to demonstrate the potential impact of this cyclization

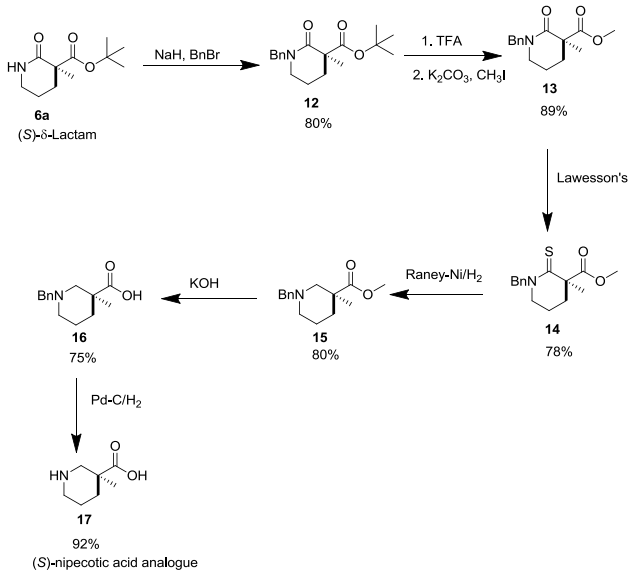
strategy by utilizing the δ-lactams to construct enantiomerically pure nipecotic acid analogues. Upon close inspection of **4a** and **6a**, it was conceived that the corresponding nipecotic acid analogues could be prepared by the selective reduction of the δ-lactam to a piperidine ring. This would allow us to prepare both enantiomers of C$^{\alpha}$-methyl-nipecotic acid analogues and establish it as a useful enantiodivergent strategy in the preparation of such analogues.



Scheme 3. Synthesis of (*R*)-C$^{\alpha}$-methyl-nipecotic acid analogue

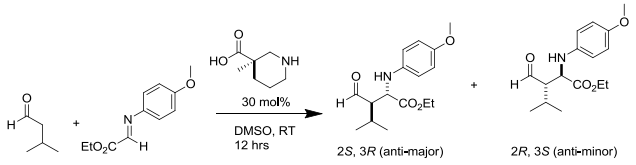
To accomplish the asymmetric synthesis of (*R*)-C$^{\alpha}$-methyl-nipecotic acid **11**, we started with the enantiomerically enriched δ-lactam **4a** as shown in Scheme 3. First, δ-lactam **4a** was benzyl protected to give **7** in good yield (81%). Then the *N*-benzylated lactam **7** was converted into thiolactam **8** employing Lawesson's reagent in good yield (80%). Thiolactam **8** was selectively reduced to the piperidine derivative **9** utilizing the Raney-Ni desulphurization technique in good yield (78%) without further purification. The saponification of **9** resulted in the *N*-benzylated-nipecotic acid analogue **10** in good yield (88%) requiring no further purification. Finally, **10** was fully deprotected by hydrogenolysis of the benzyl group resulting in pure C$^{\alpha}$-methyl-nipecotic acid **11** without further purification and in good yield (93%). Therefore, the (*R*)-nipecotic acid analogue was achieved in five overall steps requiring little purification and in very good overall yield (41%).

At this point, we wanted to use the (*S*)-δ-lactam **6a** as the key intermediate in the preparation of (*S*)-nipecotic acid analogue **17** as shown in the Scheme 4. Lactam **6a** was converted into *N*-benzyl protected lactam **12** in very good yield (80%). In the next step we discovered that the *tert*-butyl ester was not tolerated under the conditions utilized to prepare the thiolactam. To circumvent this problem, the *tert*-butyl ester was cleaved and reprotected as methyl ester **13** in one pot (89%). Lactam **13** was then converted into thiolactam **14** utilizing Lawesson's reagent in good yield (78%). Thiolactam **14** was subject to Raney-Ni desulphurization resulting in (*S*)-piperidine-3-carboxylate **15** in good yield (80%). Saponification of **15** resulted in (*S*)-*N*-benzylated nipecotic acid derivative **16** in 75% yield. Compound **16** was subjected to hydrogenation to achieve (*S*)-nipecotic acid analogue **17** in very good yield (92%). The specific rotation confirms **17** as the enantiomer of **11**. This success provides access to the (*S*)-nipecotic acid analogue **17** with a limited number of steps and a respectable overall yield of 31%.



Scheme 4. Synthesis of (*S*)-C$^{\alpha}$-methyl-nipecotic acid analogue

With the nipecotic acids in hand, we wanted to explore the organocatalytic efficiency of (*R*)-C$^{\alpha}$-methyl-nipecotic acid **11** in Mannich type reactions. To the best of our knowledge, Zhang *et al.* are the first to test (*R*)-nipecotic acid as a catalyst in Mannich reactions.[23] They observed (*R*)-nipecotic acid to produce the Mannich product with moderate *anti*-selectivity (*anti/syn* = 78 : 22) and enantioselectivity (*anti* = 36% ee, *syn* =12% ee).[23] In this context, we wanted to envisage if the enhanced rigidity employed by an additional methyl group in **11** would play a role in the selectivity of the resulting Mannich product. We performed the same Mannich reaction tested by Zhang et al. as shown in Scheme 5 employing 30 mol % of **11** as an organocatalyst.[23] The reaction was complete within 12 h and the Mannich product was obtained upon purification in reasonable yield (78%). Chiral HPLC (Figure 1) and ^{1}H-NMR established the product as moderately *anti*-selective (*anti/syn* = 72.5:27.5), and with slightly diminished ee of *anti*-enantiomers (*anti* = 26% ee) compared to literature.



Scheme 5. C$^{\alpha}$-Methyl-nipecotic acid catalyzed Mannich reaction

It is evident from the experimental data that C$^{\alpha}$-methyl nipecotic acid **11** provides the Mannich product with approximately the same *anti/syn*-selectivity as nipecotic acid, but with slightly diminished enantiomeric excess for the *anti*-Mannich product. Based on the obtained result, we propose that C$^{\alpha}$-methyl-nipecotic acid **11** prefers the (*S*)-*cis*-enamine and has a slight preference to react with the imine at the *si*-face as shown in Figure 2.

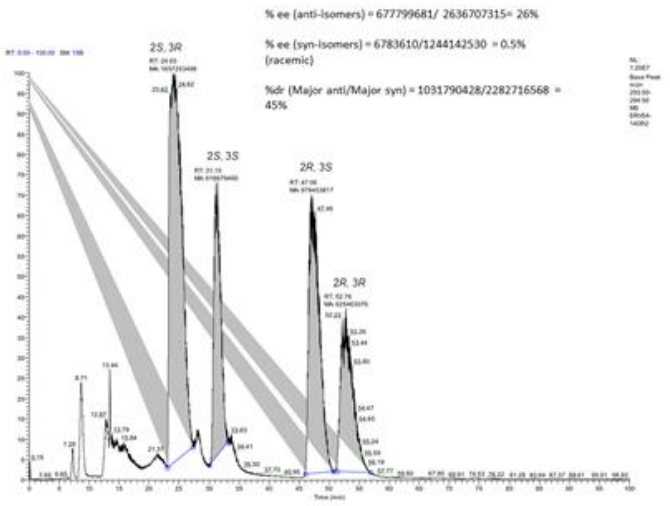


Figure 1. Chiral HPLC (Daicel Chairalcel AS-H, hexanes /*i*-PrOH = 99:1, 1.0 mL/min, λ = 254 nm) of (*R*)-C$^{\alpha}$-methylnipecotic acid **11** catalyzed Mannich product.

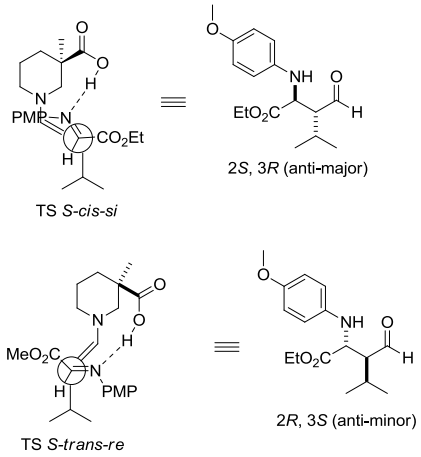


Figure 2. Proposed transition state of C$^{\alpha}$-methyl-nipecotic acid catalyzed Mannich reaction

3. Conclusions

We have optimized a highly enantioselective and enantiodivergent cyclization strategy for the preparation of δ-lactams starting with the enantiomerically enriched common intermediate **2**. This is the first reported strategy in which δ-lactams are prepared in a highly stereoselective manner simply by regulating steric and electronic factors. We believe that this straightforward approach will provide access to a wide variety of enantiomerically enriched δ-lactams. We have demonstrated that both the (*R*)- and (*S*)-δ-lactams can be readily converted into their respective nipecotic acid analogues. This success provides access to a concise and enantiodivergent approach to potentially achieve a number of highly demanding enantiomerically enriched nipecotic acid analogues. We have explored C$^{\alpha}$-methyl-nipecotic acid as a catalyst in the Mannich reaction. Our initial results show that C$^{\alpha}$-methyl-nipecotic acid provides a similar diastereomeric excess as nipecotic acid but with diminished %ee (36% ee to 26% ee) for the *anti*-diastereomers. We suspect that the increased rigidity of the piperidine ring introduced by an additional methyl group is responsible for the reduced %ee.

4. Experimental

Synthesis of diethyl-2-[3-(1,3-dioxoisoindolin-2-yl)-2-methylmalonate 1: Diester **1** was obtained from the reaction between 10 g of diethyl-2-methylmalonate (57.4 mmol), 15.40 g (57.4 mmol) of *N*-(bromopropyl)-phthalimide and 2.74 g (68.9 mmol) of NaH following a literature procedure. An amount of 12.8 g (35.4 mmol, 62%) pure **1** was obtained as colorless liquid upon purification by column chromatography (30 : 70 EtOAc/hexanes). Characterization data of **1** matched literature values.[22]

Synthesis of (*R*)-5-(1,3-dioxoisoindolin-2-yl)-2-(ethoxycarbonyl)-2-methylpentanoic acid 2: Compound **2** was prepared from 10 g of **1** (28 mmol) employing pig liver esterase (PLE) catalyzed desymmetrization following a literature procedure.[22] The resulting half-ester was purified by flash chromatography (40:60 EtOAc/hexanes) to give 6.60 g of the product as a colorless liquid (20 mmol, 68%). The % ee was determined to be 97% by chiral HPLC (Diacel Chiralpak OJ-H, 4% *i*PrOH/hexanes, flow rate = 1 mL/min, λ = 305 nm) $Rt_{(S)}$ = 54.9 min (Area = 130.13), $Rt_{(R)}$ = 58.8 min (Area = 7770.41). R_f = 0.22 (40% EtOAc/hexanes). IR (cm^{-1}) = 2983, 2937, 1773, 1747, 1697. $[\alpha]_D^{24}$ = + 5.8 (*c* 2, MeOH). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.85 (m, 2H), 7.73 (m, 2H), 4.21 (q, 2H, *J* = 7Hz), 3.71 (t, 2H, *J* = 7Hz), 1.93 (m, 2H), 1.71 (m, 2H), 1.45 (s, 3H), 1.26 (t, 3H, *J* = 7Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 176.0, 172.0, 168.0, 134.0, 132.0, 123.0, 62.0, 53.0, 38.0, 33.0, 24.0, 20.0, 14.0. HRMS [$C_{17}H_{19}NO_6Na^+$] calcd = 356.3256, found = 356.3253.

Synthesis of (*S*)-1-ethyl 3-(4-nitrobenzyl) 2-[3-(1,3-dioxoisoindolin-2-yl)propyl]-2-methylmalonate 3: A 250 mL round-bottom flask was charged with 6.41 g of **2** (19 mmol), 2.62 g of K_2CO_3 (19 mmol), 75 mL of anhydrous DMF, and a stir bar. A solution of the 4-nitrobenzyl bromide (17.1 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 × 150 mL). The combined ether layer was washed with water (8 × 150 mL) and brine (2 × 100 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The product was isolated by flash chromatography (30% EtOAc/hexanes), giving 8.10 g (17.4 mmol, 87%) pure **3** as a white solid. R_f = 0.1 (30% EtOAc/hexanes). $[\alpha]_D^{23}$ = -33.0 (*c* 1, CH_2Cl_2). mp = 66 ^{O}C. IR (cm^{-1}) = 2982, 1775, 1710. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, 2H, *J* = 8.32 Hz), 7.81 (m, 2H), 7.72 (m, 2H), 7.46 (d, 2H, *J* = 8.32 Hz), 5.22 (m, 2H), 4.15 (q, 2H, *J* = 7 Hz), 3.68 (t, 2H, *J* = 7 Hz), 1.95 (m, 2H), 1.65 (m, 2H), 1.44 (s, 3H), 1.18 (t, 3H, *J* = 7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 171.5, 168.2, 148.7, 134.0, 132.0, 128.2, 124.0, 123.3, 65.2, 61.4, 58.5, 53.0, 37.8, 33.0, 24.0, 20.0, 18.2, 13.6. HRMS [$C_{24}H_{24}N_2O_8Na^+$] calcd = 491.1425, found = 491.1422.

Synthesis of (*R*)-ethyl 3-methyl-2-oxopiperidine-3-carboxylate 4a: A volume of 1.8 mL (20 mmol) 35% hydrazine in water was added to a solution of 5.10 g (11 mmol) of **3** in 50 mL of MeOH. The mixture was heated at reflux overnight. A white precipitate was observed within 1 h of reflux. The reaction mixture was allowed to cool to room temperature, and the resulting mixture was filtered through a polypropylene 0.2 mm pore size syringe filter. An amount of 1.36g (9.9 mmol) of K_2CO_3 was added to the filtrate. The solution was allowed to reflux for 6 h, after which the solvent 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 60% Hexanes/EtOAc giving 1.5g (8.3 mmol, 75%) of **4** as a white solid. R_f = 0.35 (30% EtOAc/hexanes). $[\alpha]_D^{24}$ = + 29.2 (*c* 1, CH_2Cl_2). mp = 65 ^{O}C. IR (cm^{-1}) = 3219.6, 2940.4, 2871.9, 1726.5, 1655.5. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.25 (bs, 1H), 4.2 (m, 2H), 3.36 (m, 2H), 2.26 (m, 1H), 1.84 (m, 2H), 1.73 (m, 1H), 1.50 (s, 3H), 1.27 (t, 3H, *J* = 7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 173.6, 172.0, 61.2, 50.3, 42.3, 33.0, 22.4, 90.4, 14.0. HRMS [$C_9H_{15}NO_3Na^+$] calcd = 208.0944, found = 208.0944.

Synthesis of (*S*)-1-*tert*-butyl 3-ethyl 2-methyl-2-(3-(1,3-dioxoisoindolin-2-yl)propyl)malonate 5: A volume of 600 µL conc. H_2SO_4 was added to a solution of 2 g of **2** (6 mmol) in 30 mL of CH_2Cl_2 in a 100 mL sealed tube. The solution was cooled to -7 ºC. A volume of 6 mL of 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 2h 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 1M NaOH (50 mL). The CH_2Cl_2 layer was dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed (40% EtOAc/hexanes), giving 2 g (5.1 mmol, 87%) of **5** as a white solid. R_f = 0.53 (40% EtOAc/hexanes). $[\alpha]_D^{23}$ = -5.2 (*c* 1, MeOH). MP = 77 ^{O}C. IR (cm^{-1}): 2976.2, 2936.4, 1771.3, 1712.5. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.84 (m, 2H), 7.71 (m, 2H), 4.18 (m, 2H), 3.74 (m, 2H), 1.91 (m, 2H), 1.61 (m, 2H), 1.48 (s, 9H), 1.39 (s, 3H), 1.28 (t, 3H, *J* = 7 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) 172.3, 171.03, 168.3, 134.0, 132.1, 123.2, 81.5, 61.1, 54.0, 38.1, 34.7, 28.0, 25.3, 20.0, 14.0. HRMS [$C_{21}H_{27}NO_6Na^+$]: calcd = 412.1730, found = 412.1730.

Synthesis of (*S*)-*tert*-butyl 3-methyl-2-oxopiperidine-3-carboxylate 6a: A volume of 398 µL (4.4 mmol) 35% hydrazine in water was added to a solution of 1.50 g (4 mmol) of **5** in 25 mL of MeOH. The mixture was heated at reflux overnight. A white precipitate was observed within an hour of reflux. The reaction mixture was allowed to cool to RT and the solution was filtered. An amount of 0.55 g of K_2CO_3 (4 mmol) was added to the filtrate, and the solution was allowed to reflux for another 6 h. The solvent was evaporated under reduced pressure and the residue 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 (3 mmol, 75%) of **6a** as a white solid. R_f (**6a**) = 0.27 (30% hexanes/EtOAc). mp = 130 ^{O}C. IR (cm^{-1}): 3218.5, 2975.6, 2938.5, 2870.8, 1726.7,1660.3. $[\alpha]_D^{23}$ = -16.2 (*c* 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 400 MHz): 6.28 (bs, 1H), 3.61 (m, 2H), 2.2 (m, 1H), 1.8 (m, 2H), 1.61 (m, 1H), 1.42 (s, 12H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 174.2, 173.9, 83.0, 51.0, 43.0, 34.0, 28.0, 20.0, 14.0. HRMS [$C_{11}H_{19}NO_3Na^+$]: calcd = 236.1257, found = 236.1258.

Synthesis of (*R*)-ethyl 1-benzyl-3-methyl-2-oxopiperidine-3-carboxylate 7: A solution of 0.30 g (1.6 mmol) of **4a** in 10 mL of anhydrous THF was added slowly to a suspension of 0.046 g NaH (1.92 mmol) in 10 mL of THF at 0 °C under an N_2 atmosphere. The reaction mixture was allowed to stir for 5 min. A volume of 210 µL (1.76 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 1h at rt. A volume of 6 mL of dry DMF was added to the reaction mixture, which continued to stir for 2 h. The reaction mixture was poured into 15 mL of H_2O. The water layer was extracted with Et_2O (3 × 25 mL). The combined ether layer was washed with water (3 × 10 mL), dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed (gradient, 15−20% EtOAc/hexanes) giving 0.36 g (1.3 mmol, 81%) of pure **7** as a colorless oil. R_f = 0.3 (20% EtOAc/hexanes). $[\alpha]_D^{24}$ = + 62.6 (*c* 2, CH_2Cl_2). IR (cm^{-1}) = 3219.6, 2940.4, 2871.9, 1726.5, 1655.5. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.29 (m, 5H), 5.0 (d, 1H, *J* = 14.24 Hz), 4.2 (m, 3H), 3.24 (m, 2H), 2.23 (m, 1H), 1.79 (m, 3H), 1.54 (s, 3H), 1.29 (t, 3H, *J* = 7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 173.6, 169.3, 137.2, 128.5, 127.8, 127.3, 61.4, 50.7, 50.4, 47.3, 33.4, 22.7, 19.4, 14.2. HRMS [$C_{16}H_{21}NO_3Na^+$] calcd = 298.1413, found = 298.1411.

Synthesis of (*S*)-ethyl 1-benzyl-3-methyl-2-thioxopiperidine-3-carboxylate 8: A 1.70 g (4.2 mmol) portion of Lawesson's reagent was added to a solution of 1.30 g (4.7 mmol) of **7** in 20 mL of anhydrous toluene under an N_2 atmosphere. The reaction mixture was heated to 95 °C and stirred for over 12 h. The reaction completion was verified by TLC (20% EtOAc/hexanes). The toluene layer was evaporated under reduced pressure, and the residue was chromatographed (20% EtOAc/hexanes) giving 0.97 g (3.3 mmol, 80%) of **8** as a colorless oil. The conversion of lactam **7** to the corresponding thiolactam **8** was confirmed by comparing the ^{13}C NMR chemical shift of the lactam **7** carbonyl carbon (173.6 ppm) to thiolactam **8** carbonyl carbon (202.5 ppm). R_f = 0.3 (20% EtOAc/hexanes). $[\alpha]_D^{22}$ = +75.2 (*c* 1, CH_2Cl_2). IR (cm^{-1}) = 2936.7, 1731.3, 1506.9. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.31 (m, 5H), 5.69 (d, 1H, *J* = 14.37 Hz), 5.04 (d, 1H, *J* = 14.37 Hz), 4.23 (m, 2H), 3.43 (m, 2H), 2.28 (m, 1H), 2.01 (m, 1H), 1.83 (m, 2H), 1.75 (s, 3H), 1.30 (t, 3H, *J* = 7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 202.5, 173.6, 135.0, 129.0, 127.7, 127.5, 61.5, 57.7, 55.5, 50.4, 32.1, 27.8, 19.4, 14.0. HRMS [$C_{16}H_{21}NO_2SNa^+$] calcd = 314.1185, found = 314.1184.

Synthesis of (*R*)-ethyl 1-benzyl-3-methylpiperidine-3-carboxylate 9: A 0.80 g portion of **8 (**2.7 mmol**)** was dissolved in 20 mL of 4:1 THF/EtOH. A 0.16 g portion of Raney-Ni slurry in water (20% by weight) was added to the solution. The solution was stirred vigorously under a H_2 atmosphere for 6 h, at which point the reaction was found to be half-complete by TLC (10% hexanes/CH_2Cl_2). The mixture was continued to stir under an H_2 atmosphere another 6 h. The reaction was found to be completed via TLC to give 0.54 g (2 mmol, 78%) of **9** as a colorless liquid. R_f = 0.35 (20% hexanes/CH_2Cl_2). $[\alpha]_D^{21}$ = + 11.8 (*c* 1, CH_2Cl_2). IR (cm^{-1}) = 2939.4, 2795.4, 1725.9. ^{1}H- NMR ($CDCl_3$, 400 MHz): 7.29 (m, 5H), 4.43 (m, 2H), 3.52 (d, 1H, *J* = 13.54 Hz), 3.40 (d, 1H, *J* = 13.59 Hz), 2.97 (bm, 1H), 2.58 (bm, 1H), 2.02 (m, 3H), 1.73 (m, 1H), 1.59 (m, 1H), 1.21 (t, 3H, J = 7 Hz), 1.16 (bs, 1H), 1.13 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 176.5, 138.2, 128.8, 127.0, 63.1, 62.0, 60.2, 54.0, 43.1, 33.2, 24.0, 23.0, 14.0. HRMS [$C_{16}H_{23}NO_2Na^+$] calcd = 284.1621, found = 284.1621.

Synthesis of (*R*)-1-benzyl-3-methylpiperidine-3-carboxylic acid 10: A 0.125 g portion of crushed LiOH powder (5.2 mmol) was added to a solution of 0.46 g (1.7 mmol) of **9** in 20 mL of 3:2 H_2O/EtOH. The reaction was stirred at rt overnight. The reaction was determined to be complete by TLC (5% MeOH/CH_2Cl_2). The mixture was acidified to pH 3 (10% HCl), and the water layer was evaporated under reduced pressure giving a colorless gummy residue. The gummy residue was triturated with 10% MeOH/CH_2Cl_2 (20 mL x 20), and the MeOH fractions were dried over $MgSO_4$. The solvent was removed under reduced pressure giving 0.36 g (1.56 mmol, 88%) of **10** as a white solid as verified by TLC and staining with bromocresol green. R_f = 0.15 (5% MeOH/CH_2Cl_2). $[\alpha]_D^{22}$ = + 19.0 (*c* 1, MeOH). IR (cm-1) = 3367.5, 2961.4, 1706.1. ^{1}H- NMR (CD_3OD, 400 MHz): δ 7.52 (m, 5H), 4.50 (d, 1H, *J* = 13.61Hz), 4.17 (d, 1H, *J* = 13.59 Hz), 3.60 (d, 1H, *J* = 13.3 Hz), 3.40 (d, 1H, *J* = 13.3 Hz), 3.10 (m, 1H), 2.80 (d, 1H, *J* = 13.40 Hz), 2.20 (d, 1H, *J* = 13.40 Hz), 1.98 (m, 1H), 1.80 (m, 1H), 1.54 (m, 1H), 1.2 (s, 3H). ^{13}C-NMR (CD_3OD, 100 MHz): δ 178.1, 132.0, 131.2, 130.4, 130.3, 62.1, 57.7, 55.0, 43.4, 33.0, 24.1, 22.1. HRMS [$C_{14}H_{19}NO_2Na^+$] calcd = 256.1308, found = 256.1309.

Synthesis of (*R*)-3-methylpiperidine-3-carboxylic acid (11): A 0.30 g (1.3 mmol) portion of **10** was dissolved in 15 mL of MeOH and added to 0.06 g Pd/C (20% 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 0.185 g (1.29 mmol, 93%) of **11** as a white solid. mp = 90 ^{O}C, $[\alpha]_D^{24}$ = +1.2 (*c* 1, MeOH), R_f = 0.08 (5% MeOH/CH_2Cl_2). IR (cm^{-1}) = 3374.7, 2959.4, 1706.1. ^{1}H-NMR (CD_3OD, 400 MHz): δ 3.53 (d, 1H, *J* = 12.56 Hz), 3.28 (m, 1H), 2.97 (m, 1H), 2.83 (d, 1H, *J* = 12.56 Hz), 2.19 (d, 1H, *J* = 12.56 Hz), 1.88 (m, 1H), 1.69 (m, 1H), 1.58 (m, 1H), 1.27 (s, 3H). ^{13}C-NMR (CD_3OD, 100 MHz): δ 178.5, 50.10, 44.3, 41.4, 33.5, 23.5, 21.0. ESI-MS [$C_7H_{13}NO_2H^+$] calcd = 143.1, found = 144.1. We could not perform HRMS analysis due to the molecular weight being lower than the detection limit of the instrument.

Synthesis of (*S*)-*tert*-butyl 1-benzyl-3-methyl-2-oxopiperidine-3-carboxylate 12: A solution of 1.0 g (4.7 mmol) of **6a** in 20 mL of anhydrous THF was added slowly to a suspension of 0.14 g NaH (5.6 mmol) in 10 mL of THF at 0 °C under an N_2 atmosphere. The reaction mixture was allowed to stir for 5 min. A volume of 0.63 µL (5.2 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 20 mL of dry DMF was added to the reaction mixture, which continued to stir for 2 h. The reaction mixture was poured into 15 mL of H_2O. The water layer was extracted with Et_2O (3 × 25 mL). The combined ether layer was washed with water (3 × 10 mL), dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed (gradient, 15−20% EtOAc/hexanes) giving 1.20 g (3.8 mmol, 80%) of pure **12** as a white solid. R_f = 0.32 (20% EtOAc/hexanes). $[\alpha]_D^{24}$ = - 64.2 (*c* 1, $CHCl_3$). mp = 108 ^{O}C IR (cm^{-1}) = 2977.8, 2933.4, 1727.5, 1625.9. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.28 (m, 5H), 5.04 (d, 1H, *J* = 14.54 Hz), 4.16 (d, 1H, *J* = 14.54 Hz), 3.22 (m, 2H), 2.21 (m, 1H), 1.76 (m, 3H), 1.47 (m, 12H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 173.0, 170.2, 137.4, 128.5, 128.0, 127.3, 81.4, 51.3, 50.5, 47.4, 33.5, 28.0, 22.3, 20.0. HRMS [$C_{18}H_{25}NO_3Na^+$] calcd = 326.1726, found = 326.1728.

Synthesis of (*S*)-methyl 1-benzyl-3-methyl-2-oxopiperidine-3-carboxylate 13: A volume of 3 mL TFA was added to a solution of 1 g **12** (3.2 mmol) in 25 mL CH_2Cl_2. The reaction was continued to stir over 2 h at ambient temperature. At which point the reaction was found to be completed as evident by TLC and ESI-MS. The methylene chloride layer was evaporated and the residue was dissolved in 20 mL of DMF. An amount of 0.50 g (3.6 mmol) K_2CO_3 was added to the solution, followed by, an amount of 0.91 g (6.4 mmol) of CH_3I. The reaction was continued to stir under N_2 atmosphere over 3h at which point the reaction was found to be completed by TLC. The reaction mixture was poured into 50 mL of H_2O. The water layer was extracted with Et_2O (3 x 50 mL). The combined ether layer was extracted with water, washed with brine, dried over $MgSO_4$, and evaporated out to dryness giving 0.74 g (2.85 mmol, 89%) of pure **13** as a colorless oil. $[\alpha]_D^{22}$ = – 40.0 (*c* 0.7, $CHCl_3$). R_f = 0.29 (20% EtOAc/hexanes). IR (cm^{-1}) = 2948.6, 1730.8, 1634.6. ^{1}H-NMR ($CDCl_3$, 400 MHz) 7.30 (m, 5H), 4.81 (d, 1H, *J* = 14.27 Hz), 4.41 (d, 1H, *J* = 14.27 Hz), 3.74 (s, 3H), 3.24 (m, 2H), 2.25 (m, 1H), 1.77 (m, 3H), 1.54 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 174.4, 169.8, 137.2, 128.6, 127.8, 127.3, 52.3, 50.7, 50.5, 47.3, 33.4, 22.9, 19.7. HRMS [$C_{15}H_{19}NO_3Na^+$] calcd = 284.1257, found = 284.1258.

Synthesis of (*R*)-methyl 1-benzyl-3-methyl-2-thioxopiperidine-3-carboxylate 14: A 1.03 g (2.5 mmol) portion of Lawesson's reagent was added to a solution of 0.70 g (2.7 mmol) of **13** in 20 mL of anhydrous toluene under a N_2 atmosphere. The reaction mixture was heated to 95 °C and stirred over 12 h. The reaction completion was verified by TLC (20% EtOAc/hexanes). The toluene layer was evaporated under reduced pressure, and the residue was chromatographed (20% EtOAc/hexanes) giving 0.58 g (2.1 mmol, 78%) of **14** as colorless oil. The conversion of lactam **13** to the corresponding thiolactam **14** was confirmed by comparing the ^{13}C-NMR chemical shift of the lactam **13** carbonyl carbon (173.6 ppm) to the thiolactam **14** carbonyl carbon (202.3 ppm). R_f = 0.33 (20% EtOAc/hexanes). $[\alpha]_D^{22}$ = - 15.7 (*c* 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.33 (m, 5H), 5.35 (m, 2H), 3.76 (s, 3H), 3.42 (m, 2H), 2.30 (m, 1H), 1.92 (m, 3H), 1.75 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 202.3, 174.1, 135.3, 128.8, 127.7, 127.5, 58.0, 56.1, 52.7, 50.4, 32.4, 27.7, 19.3. HRMS [$C_{15}H_{19}NO_2SNa^+$] calcd = 300.1028, found = 300.1029.

Synthesis of (*S*)-methyl 1-benzyl-3-methylpiperidine-3-carboxylate 15: A 0.40 g portion of **14 (**1.4 mmol**)** was dissolved in 20 mL of 4:1 THF/EtOH. A 0.08 g portion of Raney-Ni slurry in water (20% by weight) was added to the solution. The solution was stirred vigorously under a H_2 atmosphere for 6 h at which point the reaction was found to be half-complete by TLC (10% hexanes/CH_2Cl_2). The mixture was continued to stir under H_2 atmosphere for another 6 h. The reaction was found to be completed via TLC to give 0.27 g (1.12 mmol, 80%) of **15** as a colorless liquid. R_f = 0.33 (20% hexanes/CH_2Cl_2). $[\alpha]_D^{23}$ = - 5.0 (*c* 0.8, $CHCl_3$). IR (cm^{-1}) = 2954.8, 2794.6, 1729.6. ^{1}H- NMR ($CDCl_3$, 400 MHz): 7.26 (m, 5H), 3.66 (s, 3H), 3.53 (d, 1H, *J* = 13.01 Hz), 3.40 (d, 1H, *J* = 13.01 Hz), 2.94 (m, 1H), 2.59 (m, 1H), 2.09 (m, 2H), 1.92 (m, 1H), 1.73 (m, 1H), 1.60 (m, 1H), 1.14 (m, 4H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 176.9, 138.6, 128.7, 127.9, 126.8, 62.9, 61.7, 54.0, 51.4, 43.3, 33.3, 23.9, 22.9. HRMS [$C_{15}H_{21}NO_2Na^+$] calcd = 270.1464, found = 270.1466.

Synthesis of (*S*)-1-benzyl-3-methylpiperidine-3-carboxylic acid 16: A 0.89 g portion of crushed KOH powder (16 mmol) was added to a solution of 0.20 g (0.8 mmol) of **15** in 20 mL of EtOH. The reaction was allowed to reflux overnight. The reaction was determined to be complete by TLC (5% MeOH/CH_2Cl_2). The mixture was acidified to pH 3 (10% HCl), and the water layer was evaporated under reduced pressure giving a colorless gummy residue. The gummy residue was triturated with 10% MeOH/CH_2Cl_2 (20 mL x 20), and the MeOH fractions were dried over $MgSO_4$. The solvent was removed under reduced pressure giving 0.14 g (0.6 mmol, 75%) of **16** as a white wax. $[\alpha]_D^{22}$ = - 9.5 (*c* 1, MeOH). Characterization data of **16** matched that of **10**.

Synthesis of (*S*)-3-methylpiperidine-3-carboxylic acid 17: A 0.30 g (1.3 mmol) portion of **10** was dissolved in 15 mL of MeOH and added to 0.06 g Pd/C (20% 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 0.185 g (1.29 mmol, 93%) of **17** as an oil. $[\alpha]_D^{24}$ = -1.5 (*c* 1, MeOH). Characterization data of **17** matched that of **11**.

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