Tetrahedron: *Asymmetry* 26 (2015) 1292–1299

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

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

Souvik Banerjee, Emily R. Vogel, Daniel Hinton, Michael Sterling, Douglas S. Masterson *

The University of Southern Mississippi, Department of Chemistry and Biochemistry, 118 College Drive #5043, Hattiesburg, MS 39406, USA

ARTICLE INFO

Article history:
Received 21 September 2015
Accepted 28 September 2015
Available online 21 October 2015

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.

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 the 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.

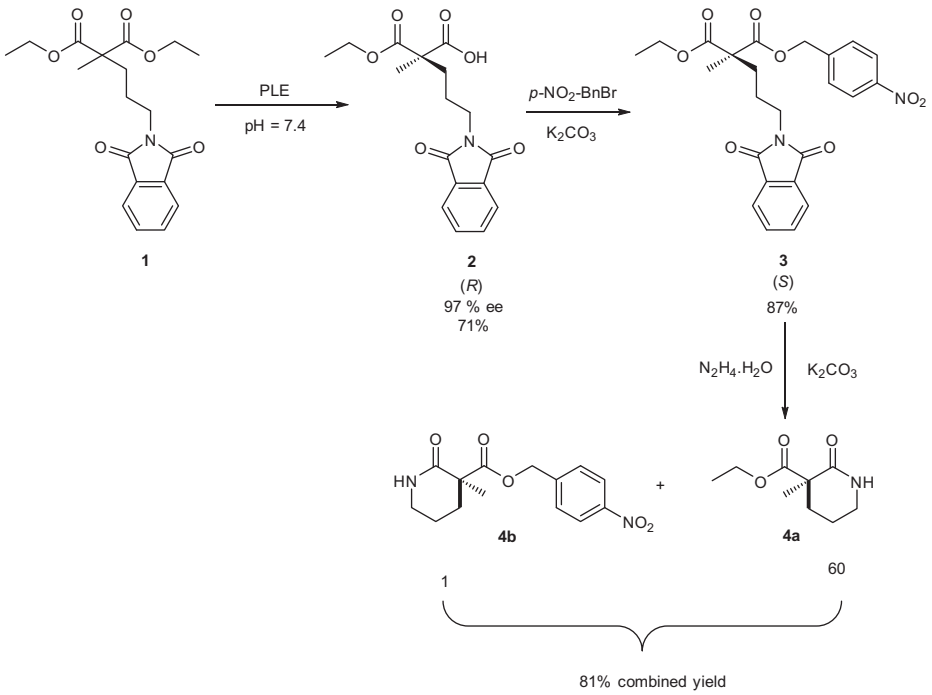
We have recently demonstrated that γ-lactams can be readily prepared by a stereoselective cyclization strategy.[21] These corresponding γ-lactams were then readily converted into highly optically enriched β-proline derivatives.[21] Hence, we wanted to employ this cyclization strategy to prepare δ-lactams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

* Corresponding author. Tel.: +1 601 266 4714; fax: +1 601 266 6075.
E-mail address: douglas.masterson@usm.edu (D.S. Masterson).

http://dx.doi.org/10.1016/j.tetasy.2015.09.014
0957-4166/



Scheme 1. Synthesis of δ-lactams.

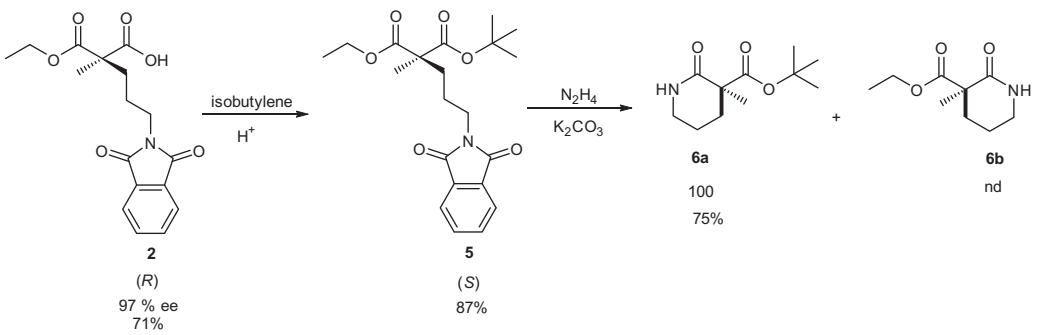
3. In our previous study, we witnessed that the *para*-NO_2-benzyl ester readily undergoes stereoselective cyclization upon removal of the phthalimide protecting group. Upon treatment of **3** with hydrazine hydrate, a cyclization took place resulting in δ-lactams **4a**, and **4b** as shown in Scheme 1. The ratio of **4a**:**4b** was 60:1 as determined by ^{1}H NMR. Therefore, the results show a high propensity toward cyclization along with a high selectivity to form δ-lactam **4a**.

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.

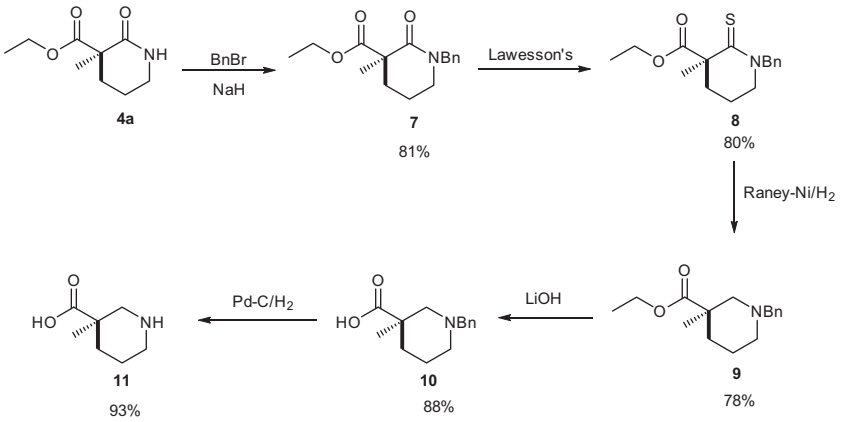
We decided to further explore this cyclization strategy to obtain **4b** as the major product. The ability to construct **4b** as the major product would provide access to a useful enantiodivergent strategy to prepare δ-lactams. However, in our previous study a Hammet study demonstrated the difficulties 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.

From a steric congestion standpoint, the ethyl ester in **5** should be more accessible toward 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.

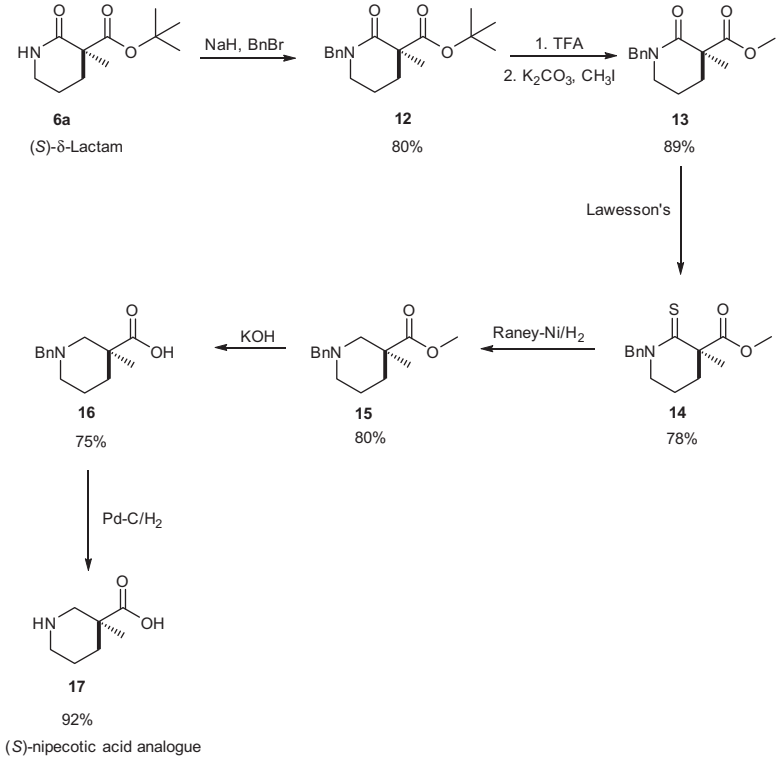
Over the last few years, C^{α}-methyl-nipecotic acid has served as an important structural entity in a number of synthetic and natural therapeutic lead compounds. For example, a group of scientists from Merck have discovered a potent NK_1 receptor antagonist, where (*R*)-C^{α}-methyl-nipecotic acid is 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 has 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



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



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

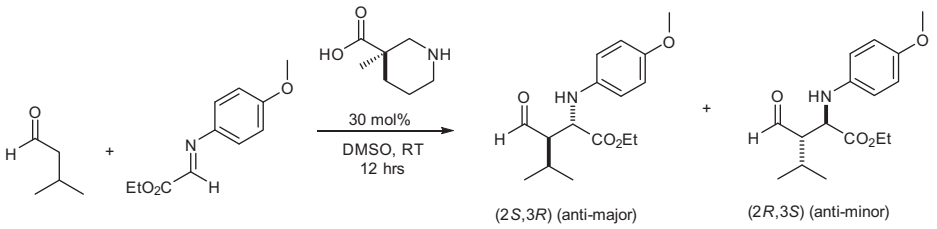


Scheme 4. Synthesis of (*S*)-C$^{\alpha}$-methyl-nipecotic acid analogue.

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.

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



Scheme 5. C^{α}-Methyl-nipecotic acid catalyzed Mannich reaction.

(78%). Thiolactam **14** was subject to Raney-Ni desulfurization 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%.

With the nipecotic acids in hand, we wanted to explore the organocatalytic efficiency of (*R*)-C^{α}-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 (Fig. 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 the literature.

It is evident from the experimental data that C^{α}-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^{α}-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.

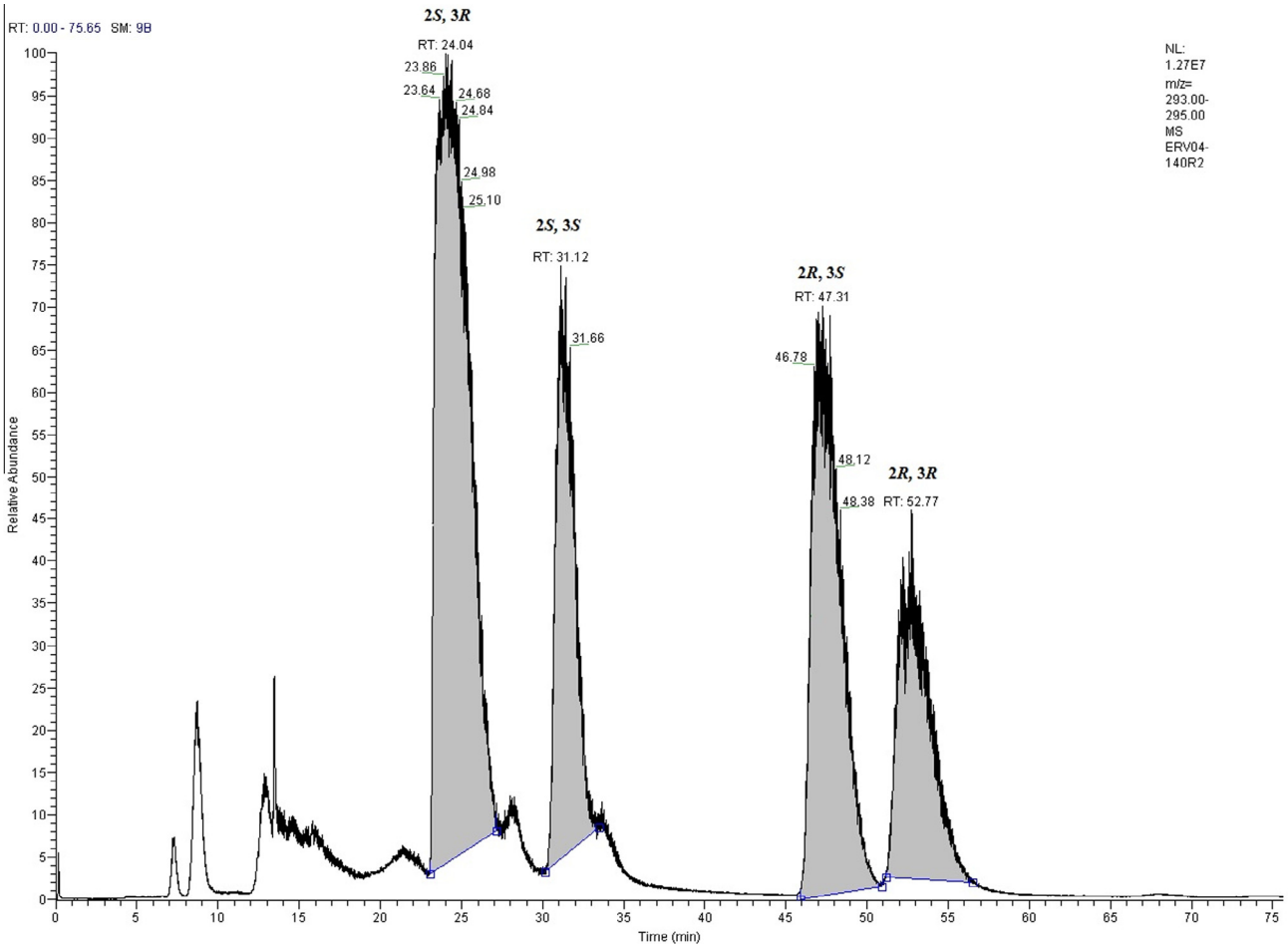


Figure 1. Chiral HPLC (Daicel Chairalcel AS-H, hexanes/*i*-PrOH = 99:1, 1.0 mL/min) of (*R*)-C^{α}-methylnipecotic acid **11** catalyzed Mannich product.

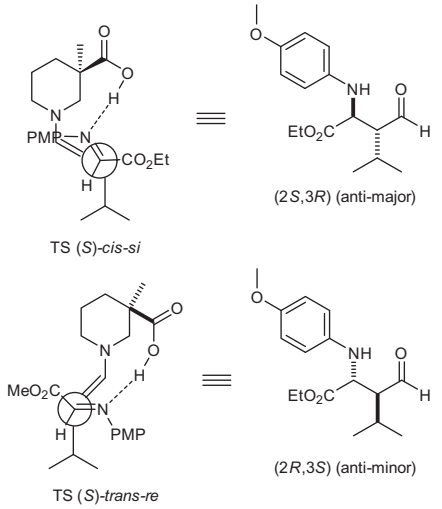


Figure 2. Proposed transition state of C^{α}-methyl-nipecotic acid catalyzed Mannich reaction.

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^{α}-methyl-nipecotic acid as a catalyst in the Mannich reaction. Our initial results show that C^{α}-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

4.1. 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 a colorless liquid upon purification by column chromatography (30:70 EtOAc/hexanes). Characterization data of **1** matched literature values.[22]

4.2. 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) $R_{t(S)}$ = 54.9 min (area = 130.13), $R_{t(R)}$ = 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* = 7 Hz), 3.71 (t, 2H, *J* = 7 Hz), 1.93 (m, 2H), 1.71 (m, 2H), 1.45 (s, 3H), 1.26 (t, 3H, *J* = 7 Hz). ^{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.

4.3. Synthesis of (*S*)-1-ethyl 3-(4-nitrobenzyl) 2-[3-(1,3-dioxoisoindolin-2-yl)propyl]-2-methylmalonate 3

A 250 mL round-bottomed 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 °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.

4.4. 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 1.36 g (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 1.5 g (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 °C. IR (cm^{-1}) = 3219.6, 2940.4, 2871.9, 1726.5, 1655.5. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.25 (br s, 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.

4.5. 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 concd 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 °C. 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 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 M 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 °C. IR (cm^{-1}): 2976.2, 2936.4, 1771.3, 1712.5. ^1H 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 ($CDCl_3$, 100 MHz) 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.

4.6. 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 °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). ^1H NMR ($CDCl_3$, 400 MHz): 6.28 (br s, 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.

4.7. 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 1 h 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. ^1H 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.

4.8. 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. ^1H 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.

4.9. 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. ^1H 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 (br m, 1H), 2.58 (br m, 1H), 2.02 (m, 3H), 1.73 (m, 1H), 1.59 (m, 1H), 1.21 (t, 3H, J = 7 Hz), 1.16 (br s, 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.

4.10. 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 × 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. ^1H NMR (CD_3OD, 400 MHz): δ 7.52 (m, 5H), 4.50 (d, 1H, *J* = 13.61 Hz), 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.

4.11. 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 °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. ^1H 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.

4.12. 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 °C IR (cm^{-1}) = 2977.8, 2933.4, 1727.5, 1625.9. ^1H 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.

4.13. 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 3 h 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 × 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. ^1H 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.

4.14. 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, $CHCl_3$). ^1H 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.

4.15. 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. ^1H 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.

4.16. 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 × 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**.

4.17. 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**.

Acknowledgements

D.S.M. would like thank the National Science Foundation for a CAREER award (MCB-0844478). E.R.V. is grateful to the National Science Foundation for a GK-12 fellowship (NSF-GK12 0947944). We are thankful to the National Science Foundation for instrument grants providing mass spectrometry and NMR facilities used in this

research (CHE-0639208, DBI-0619455, CHE-0840390) and the Department of Chemistry and Biochemistry at USM for continued support of our programs.

References

1. Oguri, H.; Mizoguchi, H.; Oikawa, H.; Ishiyama, A.; Iwatsuki, M.; Otoguro, K.; Ōmura, S. *Beilstein J. Org. Chem.* **2012**, *8*, 930–940.
2. Mizoguchi, H.; Oguri, H.; Tsuge, K.; Oikawa, H. *Org. Lett.* **2009**, *11*, 3016–3019.
3. Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 8198–8207.
4. Dutta, S.; Higginson, C. J.; Ho, B. T.; Rynearson, K. D.; Dibrov, S. M.; Hermann, T. *Org. Lett.* **2009**, *12*, 360–363.
5. Nishio, Y.; Kimura, H.; Sawada, N.; Sugaru, E.; Horiguchi, M.; Ono, M.; Furuta, Y.; Sakai, M.; Masui, Y.; Otani, M.; Hashizuka, T.; Honda, Y.; Deguchi, J.; Nakagawa, T.; Nakahira, H. *Biorg. Med. Chem.* **2011**, *19*, 5490–5499.
6. Nishio, Y.; Kimura, H.; Tosaki, S.; Sugaru, E.; Sakai, M.; Horiguchi, M.; Masui, Y.; Ono, M.; Nakagawa, T.; Nakahira, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7246–7249.
7. Huffman, M. A.; Smitrovich, J. H.; Rosen, J. D.; Boice, G. V. N.; Qu, C.; Nelson, T. D.; McNamara, J. M. *J. Org. Chem.* **2005**, *70*, 4409–4413.
8. Andersen, K. E.; Lau, J.; Lundt, B. F.; Petersen, H.; Huusfeldt, P. O.; Suzdak, P. D.; Swedberg, M. D. B. *Biorg. Med. Chem.* **2001**, *9*, 2773–2785.
9. Shintani, R.; Murakami, M.; Hayashi, T. *Org. Lett.* **2008**, *11*, 457–459.
10. Zhang, J.; Zhang, P.; Liu, X.; Fang, K.; Lin, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3769–3773.
11. Thai, K.; Wang, L.; Dudding, T.; Bilodeau, F. O.; Gravel, M. *Org. Lett.* **2010**, *12*, 5708–5711.
12. Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. *J. Org. Chem.* **2010**, *75*, 3900–3903.
13. Chen, Z.; Lin, L.; Chen, D.; Li, J.; Liu, X.; Feng, X. *Tetrahedron Lett.* **2010**, *51*, 3088–3091.
14. Zhou, C. Y.; Che, C. M. *J. Am. Chem. Soc.* **2007**, *129*, 5828–5829.
15. Patil, N. T.; Huo, Z.; Bajracharya, G. B.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 3612–3614.
16. Fiorelli, C.; Savoia, D. *J. Org. Chem.* **2007**, *72*, 6022–6028.
17. Vervisch, K.; D'hooghe, M.; Rutjes, F. P. J. T.; De Kimpe, N. *Org. Lett.* **2012**, *14*, 106–109.
18. Albrecht, A.; Morana, F.; Fraile, A.; Jørgensen, K. A. *Chem. Eur. J.* **2012**, *18*, 10348–10354.
19. Lei, A.; Chen, M.; He, M.; Zhang, X. *Eur. J. Org. Chem.* **2006**, *2006*, 4343–4347.
20. Szőllősi, G. R.; Szőri, K. I.; Bartók, M. I. *J. Catal.* **2008**, *256*, 349–352.
21. Banerjee, S.; Smith, J.; Smith, J.; Faulkner, C.; Masterson, D. S. *J. Org. Chem.* **2012**, *77*, 10925–10930.
22. Banerjee, S.; Wiggins, W. J.; Geoghegan, J. L.; Anthony, C. T.; Woltering, E. A.; Masterson, D. S. *Org. Biomol. Chem.* **2013**, *11*, 6307–6319.
23. Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H. Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2007**, *130*, 875–886.