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EFFICIENT SYNTHESIS OF METHYL (*S*)-4-(1-METHYLPYRROLIDIN-2-YL)-3-OXOBUTANOATE AS THE KEY INTERMEDIATE FOR TROPANE ALKALOID BIOSYNTHESIS WITH OPTICALLY ACITVE FORM

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Abstract – Methyl (*S*)-4-(1-methylpyrrolidin-2-yl)-3-oxobutanoate has been synthesized for enzymatic studies on cyclization enzymes during cocaine biosynthesis in *Erythroxylum coca* plants. During the present new synthesis, L-proline was first protected with Cbz group and reduced to chiral amino alcohol, which were then followed by Swern oxidation, Wittig reaction and decarboxylative condensation. At the last step, *N*-methylamino acid precursor was treated with 1,1'-carbonyldiimidazole followed by reacting with methyl potassium malonate to give the 3-oxobutanoate in 54% overall yield. This new strategy has proven to avoid obvious racemization of the L-proline chiral center during the synthesis. In addition, six of the eight synthesis steps were performed via GAP chemistry/technology without the use of column chromatography for purification.

Alkaloids are nitrogen containing heterocyclic metabolites that are often derived from amino acids and are commonly used as starting substrates for drug development because of their broad biological activities.[1] There are many different types of alkaloids, and humans have been taking advantage of their core heterocyclic structures for centuries for their pharmaceutical, narcotic, stimulants and toxic properties (Figure 1).[2] Tropane alkaloid biosynthesis has been of great interest to the natural product community for several decades.[3] These alkaloids contain complex core architectures, and their synthesis via traditional organic methods has been very challenging.[4] It is not currently possible to produce tropane alkaloids from simple precursors in heterologous microbial expression systems. In order for this goal to be achieved, the tropane alkaloid biosynthetic pathway must be fully defined in terms of the structural

genes and their corresponding enzymes. Searching for the enzymes and cofactors that play crucial roles in this biosynthesis, as well as identifying related key intermediates, has been an extremely challenging endeavor. One of the key intermediates in cocaine (tropane alkaloid) biosynthesis is methyl (*S*)-4-(1-methylpyrrolidin-2-yl)-3-oxobutanoate which serves as the extended polyketide utilized for the formation of the bicyclic core skeleton found in tropanes found in the *Erythroxylaceae*.[5,6] The lack of commercial availability for this compound hinders biochemical characterization studies of both the polyketide forming enzymes and the subsequent cyclization steps, making it necessary for the synthesis of this intermediate.[7]

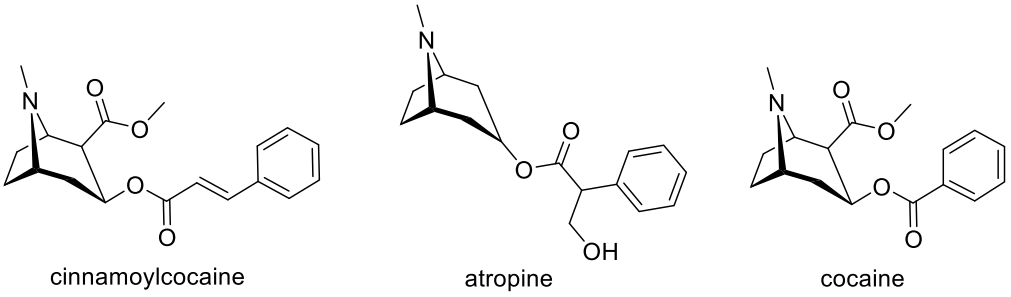
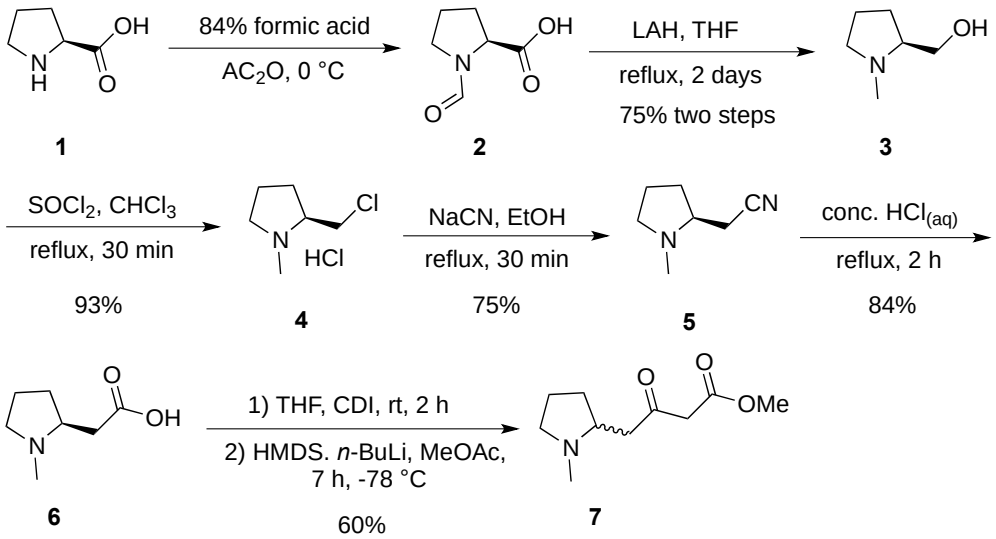


Figure 1. Representative natural products containing tropane alkaloid bicyclic core structure

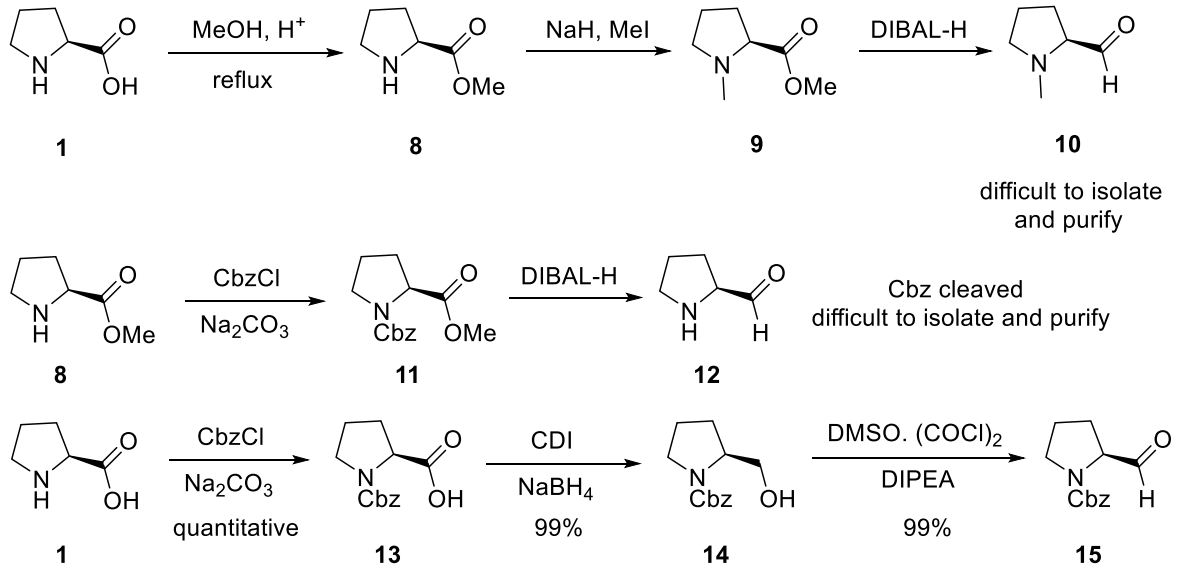
The only known synthesis of methyl (*S*)-4-(1-methylpyrrolidin-2-yl)-3-oxobutanoate was reported by Leete and coworkers in 1991.[6] The Leete synthetic method started from formyl group protection and LAH-reduction to give precursor **3** (Scheme 1); 'Halogen and cyanide anions' S_N2 displacements led to product **5**, followed by harsh acidic hydrolysis and carbonyl addition/elimination to result in the final product **7**. This synthesis was not able to control the chirality of the five-membered ring, and an overall yield of 26% was achieved in six steps (Scheme 1).



Scheme 1. Leete synthesis of 3-oxobutanoate compound

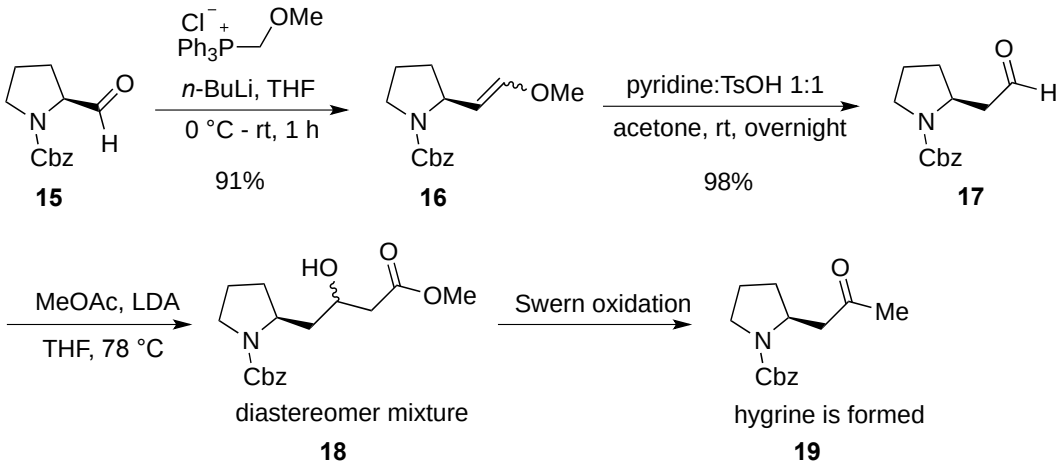
In order to obtain the asymmetric synthesis of chiral methyl (*S*)-4-(1-methylpyrrolidin-2-yl)-3-oxobutanoate, a different synthetic strategy has to be planned. L-proline resulted in becoming the first choice for serving as the starting material since a chiral center already exists in the parent structure, although the highly aqueous solubility of proline and some of its derivatives make the related total synthesis inconvenient in regard to repetitive and tedious chromatographic purification. Our strategy was planned by taking into account the following considerations: (1) to make sure the chiral center of L-proline ring is remained so as to obtain the enantiomerically pure 3-oxobutanoate; (2) to conduct the synthesis by taking advantage of our GAP chemistry[8,9] so as to minimize/avoiding tedious column chromatography; (3) to perform the synthesis under mild conditions; (4) to substantially enhance the overall chemical yield.

As shown in Scheme 2 our initial synthetic effort also began with L-proline **1** as the starting material. Proline methyl ester **8** was first generated,[10] followed by *N*-methylation with methyl iodide to afford **9**.[11] Treatment of **9** with DIBAL-H afforded the *N*-methylprolinaldehyde **10**,[12] but **10** proved difficult to isolate and to purify due to its volatility and water solubility. To remedy both properties, a new route was considered. Cbz protection of proline methyl ester **8** remedied the situation,[13] but the DIBAL reduction[12] resulted in the cleavage of the Cbz deprotected product **12**. Starting with Cbz-proline **13**, reduction with a mixed anhydride/$NaBH_4$ afforded Cbz-prolinol **14**, this reduction method is known to preserve amino acid stereochemistry and is popular for this purpose.[14] Prolinol product **14** then undergoes a Swern oxidation to afford aldehyde **15**. This condition has also been shown to avoid racemization in similar cases.[15]



Scheme 2. Initial attempts to synthesize 3-oxobutanoate

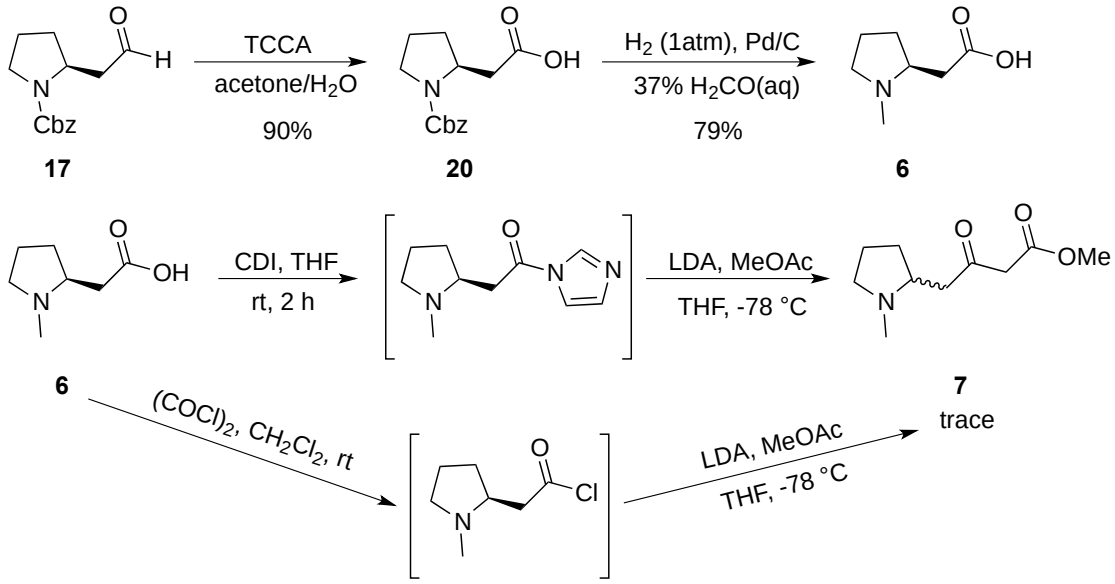
Aldehyde **15** was then subjected for a modified Wittig reaction to elongate the carbon chain (Scheme 3). Refluxing triphenylphosphine with MOMCl affords the Wittig precursor salt (methoxymethyl)triphenylphosphonium chloride.[16] Reacting this salt with *n*-butyllithium, followed by addition of **15**, affords methyl enol ether **16** after chromatographic purification as a mixture of *cis* and *trans* isomers.[17]



Scheme 3. Elongation of the carbon chain

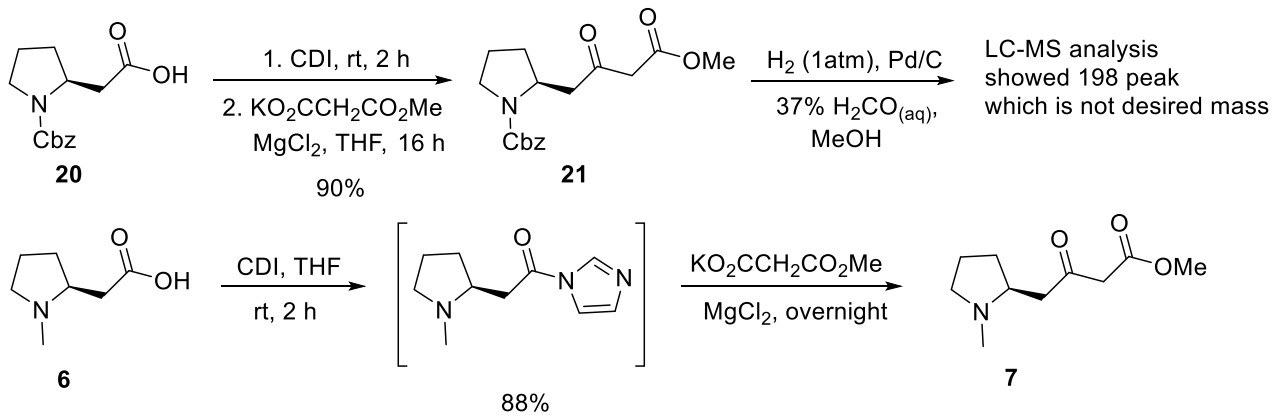
Deprotection with a 1:1 mixture of pyridine and tosic acid in acetone affords aldehyde **17**.[18] We next attempted to synthesize the oxobutanoate via an aldol condensation between aldehyde **17** and methyl acetate.[19] The alcohol **18** was fully characterized by structural analysis but was determined to be a mixture of two diastereomers. Subjection of this compound to a second Swern oxidation led to the formation of several products, one of which was hygrine **19** (presumably via decarboxylation).

To circumvent these issues, aldehyde **17** was oxidized to *N*-protected amino acid **20** with TCCA in water/acetone.[20] A one-pot hydrogenation procedure with formaldehyde can simultaneously remove the Cbz protecting group, and install the methyl group, affording amino acid **6**.[21] The plan was then to use the last step of Leete's original method to generate the oxobutanoate compound. The resulting amide was formed by reacting the carboxylic acid with 1,1'-carbonyldiimidazole which is then added to the methyl acetate enolate formed separately at -78 °C in THF with LDA; this step resulted in the formation of the desired compound **7** (Scheme 4).[7] But the yield of the final step was very poor. LC-MS analysis showed complete consumption of starting material **6** indicating efficient amide formation. Therefore, we predicted the amide intermediate generated directly from the carboxylic acid may not be reactive enough to react with the separately pre-generated enolate. Next, we converted the acid to acid chloride using oxalyl chloride to explore its reaction with the enolate.[22] Unfortunately, both above conditions gave low yields, and were hard to separate *via* column chromatography. The product was completely racemized due to the harsh conditions.



Scheme 4. Development of the final reaction

We thus continued searching for suitable procedure which can be carried out at ambient temperature to maintain the chirality until final compound **7** was formed (Scheme 5).[23] Initial studies to elongate the chain was carried out using *N*-protected amino acid **20** to ease purification process after work-up. Reacting the inexpensive available methyl potassium malonate with *in situ* generated amide from carboxylic acid **20** gave the compound **21** in 90% yield. The next step is to deprotect the *N*-protection group to give final compound. Using the previous condition for deprotection and to install methyl group simultaneously did not give the expected product. The LC-MS analysis of reaction mixture showed 198 strong peak which does not match the mass of final compound. We went back to use *N*-methylamino acid **6** to react with 1,1'-carbonyldiimidazole followed by the addition of methyl potassium malonate, pleasantly, the final product **7** was obtained in 88% yield.



Scheme 5. Successful addition of methyl acetate to *N*-methylamino acid using methyl potassium malonate

In conclusion, we have designed a new strategy for the synthesis of 3-oxobutanoate without the loss of stereochemistry in eight steps with 54% overall yield. Mild reaction conditions carefully maintained in each step allowed the compound **7** to preserve the stereochemistry. Six of these eight steps were performed via GAP chemistry without using column chromatography. The compound **7** was being used as an internal standard against the samples from tropane alkaloid plants for further analysis.

EXPERIMENTAL

Reagents were used as obtained from commercial suppliers without further purification unless otherwise specified. ACS grade hexanes, ethyl acetate, dichloromethane and methanol were used for column chromatography. Thin layer chromatography (TLC) was performed on Alumina coated silica plates from Agela Technologies and visualization was performed with UV lamp or potassium permanganate staining solution followed by heating using a hotgun or iodine on silica. Column chromatography was performed on silica gel, siliaFlash P60 40-63 μm (230-400 mesh) purchased from Silicycle. Chloroform-*d* was purchased from Cambridge Isotope Laboratories. Optical rotations were determined with AUTOPOL IV automatic polarimeter purchased from Rudolph research analytical. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL 400 MHz. Chemical shifts are given in parts per million (ppm) referenced to solvent residual proton resonance (δ = 7.26 for $CHCl_3$) and solvent carbon resonance (δ = 77.0 for $CHCl_3$). LC-MS analysis was done on LCQ FLEET (Electro spray ionization and ion trap) from Thermo Scientific.

((Benzyloxy)carbonyl)-L-proline (13)

In 150 mL of saturated Na_2CO_3 solution, L-proline (5 g, 43.43 mmol, 1 eq) is dissolved and benzyl chloroformate (6.82 mL, 47.78 mmol, 1.1 eq) is added in a dropwise manner to the above solution at 0 °C. The reaction mixture is stirred at room temperature for 3 h. CH_2Cl_2 is added to the reaction mixture and the aqueous layer is separated to which 2N HCl is added till pH drops to 2. Then the product is extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to afford **13** as yellow oil which on keeping in the fridge becomes solid. Yield 10.825 g, quantitative. $[\alpha]_D^{25}$ -105.3 (*c* 1 g/100 mL, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.68-11.39 (s, 1H), 7.45-7.27 (m, 5H), 5.27-5.07 (m, 2H), 4.52-4.29 (m, 1H), 3.69-3.40 (m, 2H), 2.34-1.81 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 178.27, 176.66, 155.69, 154.38, 136.39, 128.46, 128.34, 128.07, 127.89, 127.84, 127.60, 67.43, 67.09, 59.21, 58.57, 46.86, 46.57, 30.83, 29.36, 24.22, 23.39. MS (ESI): *m/z* calcd for $[C_{13}H_{15}NO_4 + H]^+$: 250, found: 250. Spectroscopic data agree with literature.[24]

Benzyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (14)

To a stirred solution of **13** (10.825 g, 43.43 mmol, 1 eq) in THF was added 1,1'-carbonyldiimidazole (9.365 g, 57.76 mmol, 1.33) and the reaction mixture is stirred for 15 min at room temperature. $NaBH_4$

(2.743 g, 72.52 mmol, 1.67 eq) in 60 mL H_2O is added slowly and let it stir for 30 min. Reaction mixture is quenched with 1N HCl till the pH drops to 2 and the solution is extracted with EtOAc. The combined extracts were washed with aq. $NaHCO_3$, brine, dried over $MgSO_4$ and passed through a short pad of silica to afford yellow oil. Yield 10.116 g, 99%. $[\alpha]_D^{25}$ -40.1 (*c* 1 g/100 mL, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.27 (m, 5H), 5.16-5.06 (m, 2H), 4.34-4.03 (bs, 1H), 4.01-3.86 (m, 1H), 3.71-3.57 (d, *J* = 5.2, 2H), 3.55-3.44 (m, 1H), 3.42-3.32 (m, 1H), 2.04-1.71 (bm, 3H), 1.68-1.55 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 156.88, 136.37, 128.37, 127.92, 127.75, 67.06, 66.51, 60.48, 47.15, 28.37, 23.86. MS (ESI): *m/z* calcd for $[C_{13}H_{17}NO_3 + H]^+$: 236, found: 236. Spectroscopic data agree with literature.[25]

Benzyl (*S*)-2-formylpyrrolidine-1-carboxylate (15)

A 100 mL flame-dried Schlenk flask under nitrogen atmosphere was charged with oxalyl chloride (1.64 mL, 19.12 mmol, 1.5 eq) and 60 mL dry DCM and cooled to -78 °C using dry ice/acetone. DMSO (2.71 mL, 38.25 mmol, 3.0 eq) was added dropwise, and the reaction was stirred for 15 min. A solution of **14** (3.00 g, 12.75 mmol, 1.0 eq) in 20 mL dry DCM was added dropwise, and the reaction was stirred for 1 h. DIPEA (12 mL) was added, and the reaction was stirred for an additional hour at -78 °C, followed by slow warming until the temperature reached -10 °C. Saturated aq. NH_4Cl was slowly added to quench, and the reaction was brought to room temperature. The organic layer was washed twice with additional saturated aq. NH_4Cl, dried over $MgSO_4$, filtered, and evacuated to afford **15** as yellow oil. Cooling in the fridge overnight afforded pale yellow crystals which did not melt upon warming to room temperature. Yield 2.94 g, 99%. $[\alpha]_D^{25}$ -24 (*c* 1 g/100 mL, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (d, *J* = 4.0 Hz, 1H), 7.34-7.25 (m, 5H), 5.15-5.06 (m, 2H), 4.31-4.10 (m, 1H), 3.57-3.43 (m, 2H), 2.10-1.76 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 199.79, 155.09, 154.23, 136.22, 136.01, 128.25, 127.85, 127.69, 66.97, 65.02, 64.62, 47.04, 46.46, 27.49, 26.32, 24.22, 23.43. MS (ESI): *m/z* calcd for $[C_{13}H_{15}NO_3 + H]^+$: 234, found: 234. Spectroscopic data agree with literature.[26]

Benzyl (*S*)-2-(2-methoxyvinyl)pyrrolidine-1-carboxylate (16)

A 500 mL round-bottom flask under nitrogen atmosphere was charged with (methoxymethyl)triphenylphosphonium chloride (8.729 g, 25.46 mmol, 2 eq) and 150 mL dry THF and cooled to 0 °C. *n*-Butyllithium (9.67 mL, 2.5 M, 24.19 mmol, 1.9 eq) was added dropwise, and the reaction was stirred at 0 °C for 1 h. A solution of **15** (2.97 g, 12.73 mmol, 1.0 eq) in 20 mL dry THF was added dropwise and the reaction was stirred for an additional hour at 0 °C. The reaction mixture was quenched with saturated aq. NH_4Cl at 0 °C, diluted with DCM and extracted with DCM. The combined organic layers were separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel using 10% EtOAc/hexanes as the solvent afforded **16** as an otherwise clean mixture of cis and trans isomers as colorless oil. Yield 3.027 g, 91%. $[\alpha]_D^{25}$ -5 (*c* 1 g/100 mL, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.27 (m, 5H), 6.42 (d, *J* = 6.8 Hz, 0.57H, *trans*

isomer), 5.84 (d, *J* = 5.1 Hz, 0.27H, *cis* isomer), 5.23-4.99 (m, 2H), 4.82-4.72 (m, 0.3H, *cis* isomer), 4.71-4.64 (m, 0.7H, *trans* isomer), 4.45-4.23 (m, 1H), 3.70-3.32 (bm, 5H), 2.13-1.97 (m, 1H), 1.96-1.76 (m, 2H), 1.73-1.64 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 154.96, 154.48, 149.16, 146.36, 145.77, 141.13, 137.06, 136.91, 128.28, 128.24, 127.72, 127.66, 127.24, 126.76, 108.70, 108.18, 103.60, 103.04, 66.31, 64.92, 59.75, 59.46, 55.90, 52.74, 52.11, 46.22, 33.34, 32.73, 32.44, 24.09, 23.54, 23.37, 22.83. MS (ESI): *m/z* calcd for $[C_{15}H_{19}NO_3 + H]^+$: 262, found: 262.

Benzyl (*S*)-2-(2-oxoethyl)pyrrolidine-1-carboxylate (17)

A 250 mL round-bottom flask was charged with 100 mL acetone, pyridine (1.01 mL, 12.62 mmol, 1.1 eq), and tosic acid (2.402 g, 12.62 mmol, 1.1 eq) and was stirred until homogeneous. **16** (3 g, 11.48 mmol, 1 eq) was added, and the reaction was stirred overnight at room temperature. Roughly 80% of the solvent was evacuated, followed by dilution with DCM. The organic layer was washed twice with saturated aq. NH_4Cl solution. The combined organic layers were dried over $MgSO_4$, filtered, and evacuated to afford **17** as colorless oil. Yield, 2.782 g, 98%. $[\alpha]_D^{25}$ -9 (*c* 1 g/100 mL, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (brs, 0.6H), 9.66 (brs, 0.4H), 7.40-7.27 (m, 5H), 5.18-5.08 (m, 2H), 4.36-4.26 (m, 1H), 3.53-3.37 (m, 2H), 3.03-2.76 (m, 1H), 2.55-2.45 (m, 1H), 2.19-2.07 (m, 1H), 1.93-1.80 (m, 2H), 1.73-1.60 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 200.71, 154.78, 136.61, 128.36, 128.01, 127.86, 127.73, 66.66, 52.85, 52.10, 49.08, 48.42, 46.64, 46.26, 31.84, 31.05, 23.60, 22.82. MS (ESI): *m/z* calcd for $[C_{14}H_{17}NO_3 + H]^+$: 248, found: 248. Spectroscopic data agree with literature.[27]

(*S*)-2-(1-((Benzyloxy)carbonyl)pyrrolidine-2-yl)acetic acid (20)

A 250 mL round-bottom flask was charged with 55 mL water, 125 mL acetone, and **17** (2.5 g, 10.10 mmol, 1.0 eq). TCCA (2.584 g, 11.12 mmol, 1.1 eq) was added, and the reaction was stirred overnight at room temperature. The reaction mixture was diluted with DCM and washed twice with brine. The combined organic layers were dried over $MgSO_4$, filtered and evacuated to afford **20** as yellow crystalline solid. Yield, 2.391 g, 90%. $[\alpha]_D^{25}$ -3.5 (*c* 1 g/100 mL, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.60-9.99 (bs, 1H), 7.45-7.27 (m, 5H), 5.21-5.07 (m, 2H), 4.29-4.20 (m, 1H), 3.50-3.39 (m, 2H), 3.11-2.78 (m, 1H), 2.45-2.30 (m, 1H), 2.18-2.04 (m, 1H), 1.95-1.73 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 176.53, 154.87, 136.59, 128.42, 127.92, 127.80, 66.81, 54.31, 53.75, 46.74, 46.42, 38.95, 38.25, 31.29, 30.72, 23.44, 22.66. MS (ESI): *m/z* calcd for $[C_{14}H_{17}NO_4 + H]^+$: 264, found: 264.[28]

(*S*)-2-(1-Methylpyrrolidin-2-yl)acetic acid (6)

A 50 mL Schlenk flask was charged with **20** (2 g, 7.60 mmol), 10% Pd/C (200 mg, 10 Wt%), and 20 mL MeOH. 1.45 mL of 37% aqueous formaldehyde solution was added, and the reaction was placed under hydrogen atmosphere (balloon) and stirred for 16 h at room temperature. Filtration of the reaction mixture followed by solvent evacuation afforded **6** as white amorphous solid. Yield 0.859 g, 79%. Mp 119 °C. $[\alpha]_D^{25}$ -45 (*c* 1 g/100 mL, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.50-3.41 (m, 1H), 3.17-3.07 (m,

1H), 2.58 (s, 3H), 2.67-2.40 (m, 3H), 2.21-2.09 (m, 1H), 1.98-1.65 (bm, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 174.81, 64.39, 55.45, 39.17, 36.55, 30.10, 21.82. MS (ESI): *m/z* calcd for $[C_7H_{13}NO_2 + Na]^+$: 166, found: 166.[7]

(*S*)-4-(1-Methylpyrrolidin-2-yl)-3-oxobutanoate (7)

1,1'-Carbonyldiimidazole (622 mg, 3.84 mmol, 1.1 eq) was taken in a 25 mL flame-dried Schlenk flask which was under nitrogen atmosphere. The shlenk was charged with *N*-methylamino acid **6** (500 mg, 3.49 mmol, 1.0 eq) in THF (0.5 M) and the reaction was stirred for 3 h at room temperature. Then methyl potassium malonate (818 mg, 5.23 mmol, 1.5 eq) and $MgCl_2$ (398 mg, 4.19 mmol, 1.2 eq) were added to the above solution and the reaction mixture was stirred for 16 h. Water is added to the reaction mixture and extracted with EtOAc. The crude oil was dissolved in CH_2Cl_2 and was directly loaded onto a silica gel. Flash column with 5% MeOH in DCM afforded the target compound as yellow oil. Yield 612 mg, 88%. $[\alpha]_D^{25}$ -70 (*c* 1 g/100 mL, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 3H), 3.53 (s, 2H), 3.44-3.33 (m, 1H), 3.26-3.15 (m, 1H), 3.11-2.98 (bs, 1H), 2.91-2.80 (m, 1H), 2.53 (s, 3H), 2.57-2.44 (m, 1H), 2.30-2.17 (m, 1H), 2.03-1.80 (bm, 2H), 1.74-1.60 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 200.59, 167.36, 62.80, 56.32, 52.51, 49.09, 45.24, 40.25, 30.76, 29.68, 22.04. MS (ESI): *m/z* calcd for $[C_{10}H_{17}NO_3 + H]^+$: 200, found: 200.

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