(*R*)-α-Aminoadipic acid: an interesting chiral pool building block

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Dedicated to Prof. Ferenc Fülöp on the occasion of his 60th birthday

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Abstract
(*R*)-α-Aminoadipic acid is available on a large scale by enzymatic cleavage from cephalosporin C (CephC) in the production of 7-aminocephalosporanic acid (7-ACA). It can be converted into other interesting enantiomerically pure compounds, e.g. derivatives of (*R*)-pipecolic acid (*R*-piperidine-2-carboxylic acid), (*R*)-6-oxopiperidine-2-carboxylic acid, (*R*)-1,2,3,4-tetrahydro-pyridine-2(2*H*)-carboxylates, and other compounds obtained by further conversions of these products.

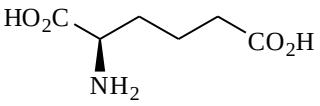
Keywords: (*R*)-α-Aminoadipic acid, (*R*)-Pipecolic acid, Vilsmeier-Haack reaction

Introduction

Amino acids are appreciated by synthetic chemists as inexpensive and versatile enantiomerically pure building blocks. Besides in the synthesis of peptides and peptidomimetics, amino acids found widespread application as starting materials or even catalysts in the synthesis of a broad range of compounds.[1] (*R*)-Configured amino acids do not occur in Nature as frequently as their (*S*)-configured enantiomers. (*R*)-Amino acids exert conformational bias, when they are incorporated e.g. in cyclic peptides.[2] Moreover, the sense of chirality also renders them interesting starting materials for synthesis.

(*R*)-α-Aminoadipic acid **1** is a constituent of penicillin N and cephalosporin C. In the semisynthesis of other penicillin and cephalosporin derivatives (*R*)-α-aminoadipic acid is first cleaved by chemical or enzymatic means to give 6-aminopenicillanic acid (6-APA) and 7-aminocephalosporanic acid (7-ACA), resp. 6-APA and 7-ACA are then acylated to give different penicillins and cephalosporins. In the case of cephalosporin C cleavage by cephalosporin acylase provides (*R*)-α-aminoadipic acid as a side product in large quantities.[3]

We therefore embarked on a project to explore, how the enantiomerically pure (*R*)-α-amino-adipic acid could be used as a building block in the preparation of other compounds. Besides the known conversion into the δ-lactam **2**, we envisaged the transformation into benzyl 1-benzyloxycarbonyl-5-formyl-1,2,3,4-tetrahydropyridine-2-carboxylate **3** and (*R*)-pipecolic acid **4**.



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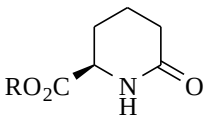
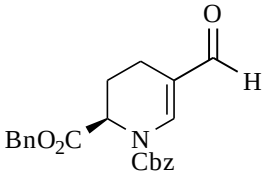


2a R = CH_3
2b R = C_2H_5



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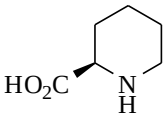


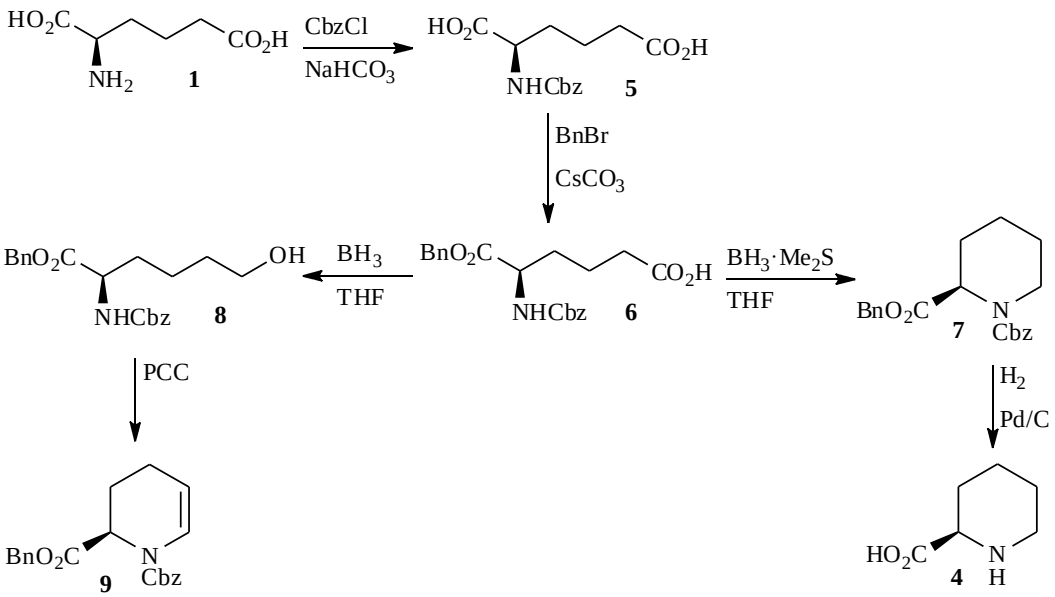
4

Pipecolic acid,[4] also known as homoproline or piperidine-2-carboxylic acid, is a naturally occurring cyclic amino acid which displays interesting and potent biological activities. The presence of (*S*)-pipecolic acid in many biologically active natural products such as the immunosuppressant FK 506,[5] rapamycin,[6] the anticancer agent VX710,[7] and the antifungal antibiotic sandramycin.[8] (*R*)-Pipecolic acid occurs in the central nervous system of mammals to control the synaptic transmission and is also a well-known intermediate in the synthesis of piperidine alkaloids. Furthermore, it is a constituent of the histone deacetylase (HDAC) inhibitor apicidin.[9,10] HDAC inhibitors hold promise as anticancer therapeutics.[11] Moreover, (*R*)-pipecolic acid has also been recently employed as a catalyst for asymmetric Mannich reactions.[12]

Like proline, pipecolic acid is also a valuable building block for the synthesis of conformationally constrained peptides.[13] Hence, a convenient access to (*R*)-pipecolic acid is of importance because it is a key constituent of bioactive molecules, a useful building block for asymmetric synthesis and a versatile organocatalyst.

Results and Discussion

Having access to (*R*)-α-aminoadipic acid from the industrial process, we focused on the synthesis of (*R*)-pipecolic acid **4**. Enantiomerically pure pipecolic acid has previously been available by different procedures.[14] We developed a new and simple synthesis of (*R*)-pipecolic starting from (*R*)-α-aminoadipic acid. The most useful amino protecting groups are the carbamates, which are extensively used for the synthesis of amino acids and other natural products. In particular, benzyl carbamates are useful for amino acid synthesis as they are resistant to a variety of reagents, can readily be cleaved and minimize the racemization of amino acids. In the course of our studies, we protected the amino group as well as selectively the α-carboxylic group of (*R*)-α-aminoadipic acid with benzyl based protective groups because a final deprotection step removes all protective groups in one step.

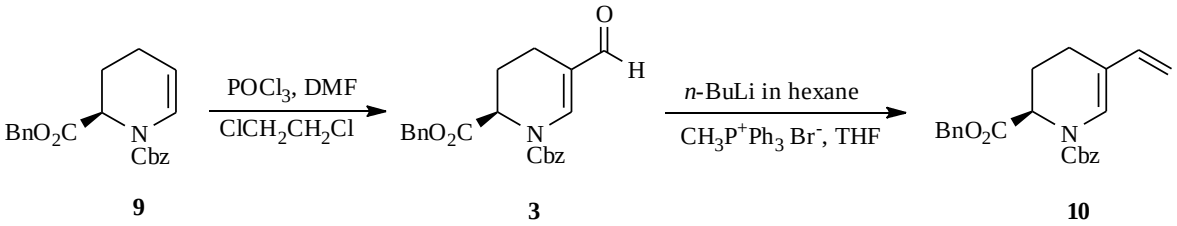


Scheme 1. Protection of (*R*)-α-aminoadipic acid **1**, synthesis of (*R*)-pipecolic acid **4**, and of the dehydro derivative **9**.

The amino group of (*R*)-α-aminoadipic acid **1** was protected with the Cbz group to give urethane **5** in 89% yield.[15] This was then selectively esterified with a benzyl ester moiety at the α-position to give **6** in 40% yield according to a literature procedure.[16] The carboxy group of intermediate **6** was then subjected to reductive cyclization on treatment with $BH_3 \cdot Me_2S$ to prepare the protected (*R*)-pipecolic acid **7** in 63% yield. Hydrogenation of **7** over Pd/C (10%) in the presence of a catalytic amount of AcOH afforded the crude product which was then purified by triturating with diethyl ether to furnish the desired product **4** in 88% yield (Scheme 1).

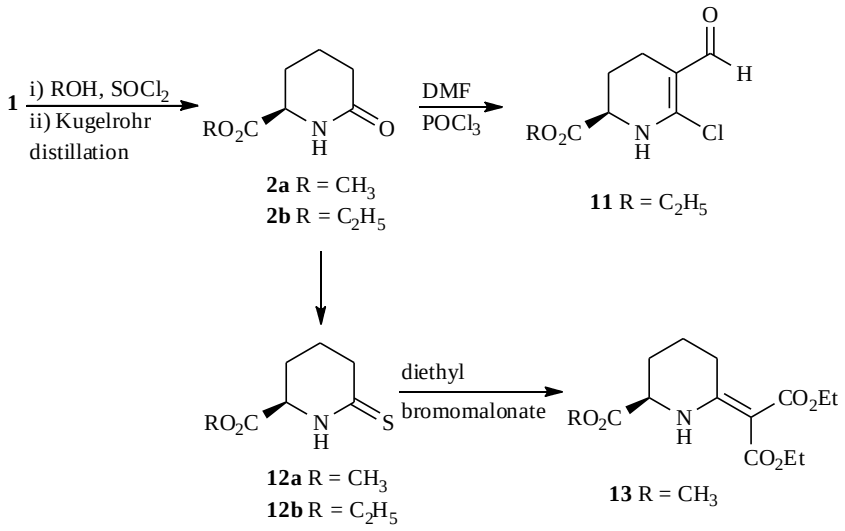
Reduction of *ent*-**6** with borane - THF is reported to afford the corresponding alcohol *ent*-**8** in 74% yield, which can be transformed into the dehydro derivative *ent*-**9** in 46% yield.[17] We followed this procedure to convert **6** to **9** in 40% total yield and used the latter compound as a starting material for a Vilsmeier-Haack reaction. In the frame of this procedure, electron rich aromatic compounds or alkenes react with an iminium salt formed *in situ* from *N*,*N*-dimethylformamide and phosphorus oxychloride. Aldehyde **3** was obtained in 73% yield and shown to be enantiomerically pure (*ee* > 99%) by chiral HPLC (Chirex (*S*)-*tert*.-leucine).

3 was subsequently used as an intermediate to synthesize various new derivatives of (*R*)-pipecolic acid. The Wittig reaction afforded product **10** where a vinyl group is introduced at C-5 of the pipecolic acid core (Scheme 2). Exemplarily, this reaction was carried out with the phosphorus ylid generated from methyl triphenylphosphonium bromide with *n*-BuLi at –78 °C to afford the vinyl substituted product **10** in 60% yield.



Scheme 2. Synthesis of formyl and vinyl derivatives of (*R*)-pipecolic acid.

(*R*)-6-Oxopipecolates **2** were prepared from (*R*)-α-aminoadipic acid by esterification and subsequent cyclization during Kugelrohr distillation in excellent yield according to a protocol described for (*S*)-6-oxopipecolic acid (*ent*-**2**).[18] Compound **11** was formed in 70% yield upon reaction of **2** under Vilsmeier-Haack conditions as described for **3** (Scheme 3).



Scheme 3. Vilsmeier-Haack formylation of **2**, thionation of **2** and further conversion.

Thiolactams **12a/b** were prepared in 80% and 56% yield, resp., by thionation of the corresponding δ-lactams **2** with 1.8 equivalents of Lawesson's reagent like described previously for gluconolactam derivatives.[19] **12a** was further treated with diethyl bromomalonate in presence of triethyl amine to produce compound **13** in 72% yield.

In summary, a simple and completely stereoconservative access to (*R*)-pipecolic acid starting from (*R*)-α-aminoadipic acid has been developed. Furthermore, the synthesis of novel (*R*)-pipecolic acid derivatives by Vilsmeier-Haack reaction and further transformations of these products lead to interesting amino acids.

Experimental Section

General. THF was dried over Na/benzophenone and DCM was dried over CaH_2. Commercially available chemicals were purchased from Sigma-Aldrich. EtOAc was distilled before use. All reactions were carried out in oven-dried glassware with magnetic stirrers under an argon atmosphere. Flash chromatography was carried out using silica gel, particle size 0.035-0.070 mm. Specific rotation of synthesized compounds was recorded on a Jasco DIP-366 digital polarimeter. ^{1}H NMR spectra were recorded on a 500 MHz Bruker DRX spectrometer in $CDCl_3$ (unless otherwise stated) referenced relative to residual $CHCl_3$ (δ = 7.26 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. ^{13}C NMR spectra were recorded on the same instrument (125.7 MHz) with total proton decoupling.

EI and CI mass spectra (including EI accurate mass measurements) were recorded using an Autospec X magnetic sector mass spectrometer with EBE geometry (Vacuum Generators, Manchester, UK) equipped with a standard EI or CI source. Samples were introduced by push rod in aluminium crucibles if not otherwise noted. Ions were accelerated by 8 kV in EI mode and 6 kV in CI mode. accurate mass measurement (or EI/CI) experiments were performed using a Fourier Transform Ion Cyclotron Resonance (ESI- or MALDI-FT-ICR) mass spectrometer APEX III (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7.0 T, 160 mm bore superconducting magnet (Bruker Analytik GmbH – Magnetics, Karlsruhe, Germany), infinity cell, and interfaced to an external (nano)ESI or MALDI ion source. Nitrogen served both as the nebulizer gas and the dry gas for ESI. Nitrogen was generated by a Bruker nitrogen generator NGM 11. Argon served as cooling gas in the infinity cell and collision gas for MS^n experiments.

***N*-Benzyloxycarbonyl-(*R*)-α-aminoadipic acid; Cbz-(*R*)-Aad(OH)-OH (5).**[15] M.p = 133-135 °C; lit.[15] m.p = 136-136.5 °C. $[\alpha]_D^{23}$ = +15.1 (c = 1, EtOH / 2 N NaOH); lit.[15] $[\alpha]_D^{23}$ = +17 (c = 2, EtOH / 2 N NaOH)

***N*-Benzyloxycarbonyl-(*R*)-α-aminoadipic acid α-benzyl ester; Cbz-(*R*)-Aad(OH)-OBzl (6).**[16] M.p = 91-93 °C; lit.[16] m.p = 90-92 °C. $[\alpha]_D^{23}$ = +13.5 (c = 1, acetone);

***N*-Benzyloxycarbonyl-(*R*)-pipecolic acid benzyl ester; Cbz-(*R*)-Pip-OBzl (7).** $BH_3 \cdot Me_2S$ (23 mL of a 2M solution in THF, 46.0 mmol) was added to a solution of protected Cbz-(*R*)-Aad(OH)-OBzl **6** (3.0 g, 8.49 mmol) in 70 mL of anhydrous THF at room temperature and the resulting mixture was stirred for 3 h (monitored by TLC). After completion of the reaction it was quenched by addition of MeOH (3 mL) and the solvents were evaporated under reduced pressure. The residue which was then purified by flash chromatography (Et_2O/PE; 3:1) to afford 1.71 g Cbz-(*R*)-Pip-OBzl (63%) as pale yellow oil. $[\alpha]_D^{23}$ = +7.4 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, conformer mixture): δ = 7.39-7.35 (m, 10H, Ar-H), 5.23-4.89 (m, 5H, Bn-CH_2, CH), 4.18-4.09 (m, 1H, CH_2), 3.14-3.00 (m, 1H, CH_2), 2.32-2.25 (m, 1H, CH_2) 1.76-1.63 (m, 3H, CH_2), 1.48-1.44 (m, 1H, CH_2), 1.31-1.24 (m, 1H, CH_2). ^{13}C NMR (125.7 MHz, $CDCl_3$, conformer mixture): δ = 171.6 (COO), 156.6/156.0 (NCOO), 136.6/136.5 (Ar-C), 135.7/135.6 (Ar-C), 127.8 (10 Ar-CH), 67.3 (Bn-CH_2), 66.8 (Bn-CH_2), 54.7 (CH), 41.9/41.8 (CH_2), 31.6

/26.8 (CH$_2$), 24.7/24.5 (CH$_2$), 20.7/20.6 (CH$_2$). $C_{21}H_{23}NO_4$ (353.41). HRMS (MALDI-FT-ICR): *m/z* = 376.15134; calcd. for $[C_{21}H_{23}NO_4Na]^+$: *m/z* = 376.15193.

(*R*)-Pipecolic acid; H-(*R*)-Pip-OH (4). A solution of compound Cbz-(*R*)-Pip-OBzl **7** (414 mg, 1.17 mmol) in dry EtOH (25 mL) was mixed with Pd/C (10%) (248 mg) and AcOH (0.3 mL) in a hydrogenation flask and then the mixture was vigorously shaken at ambient temperature for 24 h. Then the mixture was filtered through a pad of Celite. After the evaporation of the solvent under vacuum, the solid residue was dissolved in a little amount of MeOH and precipitated with Et_2O. The precipitate was collected by filtration, washed with Et_2O and dried under high vacuum to afford pure (*R*)-pipecolic acid **4** (132 mg, 88%). All the physical data match the reported values.[20] m.p = 271-273 °C; lit.[20] m.p = 271-274 °C. $[\alpha]_D^{23}$ = +26.0 (c = 1, water); lit.[20] $[\alpha]_D^{23}$ = +26.3 (c = 1, water).

(*R*)-2-(Benzyloxycarbonylamino)-6-hydroxyhexanoic benzyl ester (8).[17] Yield = 72%; $[\alpha]_D^{23}$ = +5.3 (c = 1, $CHCl_3$).

(*R*)-Benzyl 2-benzyloxycarbonyl-1,2,3,4-tetrahydropyridine-2-carboxylate (9).[17] Yield = 420 mg (56%); $[\alpha]_D^{23}$ = +4.2 (c = 1, $CHCl_3$). The ^{1}H NMR spectrum matches reported data.[17] ^{13}C NMR (125.7 MHz, $CDCl_3$, conformer mixture): δ = 170.8/170.6 (CO$_2$CH$_2$), 153.4/153.2 (NCOO), 137.1/136.0 (Ar-C), 135.6/134.4 (Ar-C), 128.5 (10 Ar-C), 124.5/124.2 (N-C=C), 105.8/105.4 (N-C=C), 67.7/67.0 (CO$_2$CH$_2$), 66.9/66.8 (CO$_2$CH$_2$), 54.1/53.8 (CH), 23.5/23.4 (CH$_2$), 18.4/18.2 (CH$_2$).

(*R*)-Benzyl 1-benzyloxycarbonyl-5-formyl-1,2,3,4-tetrahydropyridine-2-carboxylate (3). Phosphorus oxychloride (0.39 mL, 4.27 mmol) was added dropwise to DMF (0.33 mL, 4.27 mmol) at 10-20 °C over a period of 3 min and the mixture was then stirred for 20 min. After the mixture was cooled to 5 °C, 1,2-dichloroethane (3.0 mL) was added, and then a solution of **9** (150 mg, 0.42 mmol) in 1,2-dichloroethane (5 mL) was added during 30 min. The solution was stirred at 0-5 °C for 1 h and was then refluxed for 15 min. A solution of sodium acetate trihydrate (70 mg) in water (3.0 mL) was added to the cooled mixture. The mixture refluxed for 15 min and then cooled to room temperature. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous magnesium sulfate. After the drying agent was filtered off, the residue was purified by column chromatography on silica gel (*n*-hexane/AcOEt; 1:1) to give aldehyde **3** as pale yellow oil (119 mg, 73%). $[\alpha]_D^{23}$ = +24.9 (c = 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, conformer mixture): δ = 9.35/9.26 (s, 1 H, CHO), 7.94/7.77 (s, 1 H, CH), 7.42-7.36 (m, 10 H, Ar-H), 5.36-4.97 (m, 5 H, Bn-CH$_2$, CH), 2.52-2.44 (m, 2H, CH$_2$), 1.85-1.80 (m, 2H, CH$_2$). ^{13}C NMR (125.7 MHz, $CDCl_3$, conformer mixture): δ = 190.4/190.2 (CHO), 169.6/169.5 (COO), 152.4/152.4 (NCOO), 144.0/143.5 (C=CCHO), 135.1/135.0 (2 Ar-C) 128.7/128.0 (10 Ar-CH), 120.8/120.5 (C=CCHO), 69.4/69.3 (Bn-CH$_2$), 67.5/67.4 (Bn-CH$_2$), 55.3/54.9 (CH), 22.5/22.3 (CH$_2$) 15.4/15.1 (CH$_2$). $C_{22}H_{21}NO_5$ (379.41). HRMS (ESI-FT-ICR): *m/z* = 380.14921; calcd. for $[C_{22}H_{22}NO_5]^+$: *m/z* = 380.14925.

(*R*)-Benzyl 1-benzyloxycarbonyl-5-vinyl-1,2,3,4-tetrahydropyridine-2-carboxylate (10). *n*-Butyl lithium (0.1 mL, 1.6 M in hexane, 0.08 mmol) was added to a stirred solution of

triphenylmethylphosphonium bromide (79 mg, 0.08 mmol) in THF (5 mL) and the resulting mixture was stirred at room temperature for 30 min. The solution of aldehyde **3** (25 mg, 0.07 mmol) in THF (3 mL) was added dropwise to the mixture. The reaction mixture was stirred at room temperature for 1.3 h. After completion of the reaction as monitored by TLC (hexane:EE, 7:3), it was quenched by addition of water and extracted with ether. The combined ether layers were dried and concentrated to give crude product which was then purified by flash chromatography on silica gel (*n*-hexane/AcOEt; 7:3) to give product as colorless oil (15.5 mg, 60%). $[\alpha]_D^{23}$ = +43.1 (c = 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, conformer mixture): δ = 7.42-7.35 (m, 10H, Ar-H), 7.10/6.98 (s, 1H, CH), 6.41-6.27 (m, 1H, CH), 5.30-5.12 (m, 4H, Bn-CH_2), 5.04-4.97 (m, 1H, CH), 4.92-4.87 (m, 1H, CH), 4.18-4.03 (m, 1H, CH), 2.50-2.40 (m, 1H, CH_2), 2.30-2.23 (m, 1H, CH_2), 2.03-1.86 (m, 1H, CH_2), 1.60-1.50 (m, 1H, CH_2). ^{13}C NMR (125.7 MHz, $CDCl_3$, conformer mixture): δ = 170.6/170.4 (COO), 153.3/153.1 (NCOO), 136.7/136.6 (Ar-C), 135.8/135.7 (Ar-C), 135.5/135.4 (CH) 128.6/127.8 (10 Ar-CH), 125.5/125.0 (CH), 117.6/117.2 (C), 109.3/109.1 (CH_2), 68.5/68.2 (Bn-CH_2), 67.6/67.0 (Bn-CH_2), 54.2/53.9 (CH) 30.5/29.7 (CH_2), 23.2/23.0 (CH_2). $C_{23}H_{23}NO_4$ (377.43). HRMS (MALDI-FT-ICR) *m/z* = 400.15204; calcd. for $[C_{23}H_{23}NO_4Na]^+$: *m/z* = 400.15193.

(*R*)-Ethyl 6-chloro-5-formyl-1,2,3,4-tetrahydropyridine-2-carboxylate (11). A solution of anhydrous *N*,*N*-dimethylformamide (0.24 mL, 2.90 mmol) in dry chloroform (2.40 mL) was added dropwise to a stirred solution of phosphorus oxychloride (2.90 mmol, 0.44 mL) under a nitrogen atmosphere at room temp. After 30 min, a solution of 6-oxopipecolic acid ethyl ester **2b** (100 mg, 1.80 mmol) in 5 mL of dry chloroform was added. After 18 h stirring at room temperature, a solution of sodium acetate (70 mg) dissolved in water (5 mL) was slowly added. After 0.5 h, the mixture was partitioned between water and chloroform, and the aqueous phase was extracted with ethyl acetate. The organic phases were mixed and dried with anhydrous magnesium sulfate. The organic solvent was removed in vacuum and the residue was then purified by flash chromatography (*n*-hexane-AcOEt; 7:3). The product was obtained in the form of a pale yellow oil (88 mg, 70%). $[\alpha]_D^{23}$ = +2.1 (c = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3COCD_3, conformer mixture): δ = 8.98/8.03 (s, 1H, CHO), 5.27-5.24 (m, 1H, CH), 4.20 (q, 2H, *J* = 7.5, CH_2), 2.43-2.37 (m, 1H, CH_2), 2.27-2.20 (m, 1H, CH_2), 2.16-2.11 (m, 1H, CH_2), 1.98-1.92 (m, 1H, CH_2), 1.25 (t, 3H, *J* = 7.5 Hz, CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$, conformer mixture) δ 173.8/172.1 (CHO), 164.1/162.7(COO), 161.5/160.2 (C-Cl), 108.5 (C-CHO), 62.1/62.0 (CHCOO), 54.7/53.8 (CH_2), 30.2/29.7 (CH_2), 24.9/22.7 (CH_2), 15.2/14.1 (CH_3). $C_9H_{12}ClNO_3$ (217.65). HRMS (EI): *m/z* = 217.04930; calcd.: *m/z* = 217.05057.

(*R*)-Methyl 6-thioxopiperidine-2-carboxylate (12a). 6-Oxopipecolic acid methyl ester **2a** (56.9 mg, 0.12 mmol) was placed in a round bottom flask, the system was purged with anhydrous nitrogen and the compound was dissolved in anhydrous toluene (2.0 mL). Lawesson's reagent (45.0 mg, 0.11 mmol) was added to this solution. Once the reagent was added, the reaction mixture was stirred at room temperature for 15 min and then three hours at 90 ºC. After the completion of reaction (monitored by TLC) the solvent was removed under reduced pressure. The residue was then subjected to column chromatography (*n*-hexane/DCM; 7:3) to give pure

product **12a** as yellow oil (41 mg, 80%). $[\alpha]_D^{23}$ = +10.8 (c = 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.48 (br.s, 1H, NH), 4.12 (m, 1H, CH), 3.83 (s, 3H, CH_3), 2.98 (m, 1H, CH_2), 2.88 (m, 1H, CH_2), 2.28 (m, 1H, CH_2), 1.88 (m, 2H, CH_2), 1.78 (m, 1H, CH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 203.8 (CS), 169.9 (COO), 56.4 (CH), 53.1 (COO<u>C</u>H$_3$) 39.0 (CH_2), 24.1 (CH_2), 19.4 (CH_2). $C_7H_{11}NO_2S$ (173.23). HRMS (EI): *m/z* = 173.05070; calcd.: *m/z* = 173.05105.

(*R*)-Ethyl 6-thioxopiperidine-2-carboxylate (12b). The ethyl derivative was obtained from **2b**. Yield: 70 mg, 56%. $[\alpha]_D^{23}$ = +11.7 (c = 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45 (s, 1H, NH), 4.36-4.28 (m, 2H, CH_2), 4.07 (m, 1H, CH), 3.00 (m, 1H, CH_2), 2.87 (m, 1H, CH_2), 2.29 (m, 1H, CH_2), 1.87 (m, 2H, CH_2), 1.78 (m, 1H, CH_2), 1.33 (t, *J* = 10 Hz, 3H, CH_3) ; ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 203.7 (CS), 169.4 (COO), 62.4 (CH_2), 56.5 (CH), 39.0 (CH_2), 24.2 (CH_2), 19.4 (CH_2), 14.1 (CH_3). $C_8H_{13}NO_2S$ (187.26). HRMS (MALDI-FT-ICR) *m/z* = 210.05582; calcd. for $[C_8H_{13}NO_2SNa]^+$: *m/z* = 210.05592.

(*R*)-Diethyl 2-(6-(methoxycarbonyl)-piperidin-2-ylidene)malonate (13). Diethyl bromomalonate (0.2 mL, 0.33 mmol) was added to a solution of thiolactam **12a** (51 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was stirred for 2 h. Triethylamine (0.05 mL, 0.33 mmol) was added and the solution was stirred for two more hours. It was then diluted with CH_2Cl_2 and washed with 1 M aqueous HCl, the aqueous phases were extracted with CH_2Cl_2, the combined organic phase was dried, evaporated and the residue was purified by flash chromatography (*n*-hexane/AcOEt 7:3) to give **13** as yellow oil (72 mg, 72%). $[\alpha]_D^{23}$ = +3.0 (c = 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.22-4.19 (m, 4H, COOC<u>H</u>$_2$), 4.17 (m, 1H), 3.80 (s, 3H, COOC<u>H</u>$_3$), 2.67 (m, 2H, CH_2), 2.22 (m, 1H, CH_2), 1.89-1.79 (m, 3H, CH_2), 1.32-1.26 (m, 9H, C<u>H</u>$_3$). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 171.5 (<u>C</u>OOMe), 168.9 (<u>C</u>OOEt), 168.5 (<u>C</u>OOEt), 163.5 (N-<u>C</u>=C), 91.6 (N-C=<u>C</u>), 60.3 (CH), 59.5 (COO<u>C</u>H$_2$CH$_3$), 53.7 (COO<u>C</u>H$_2$CH$_3$), 52.7 (COO<u>C</u>H$_3$), 26.6 (CH_2), 25.0 (CH_2), 18.2 (CH_2), 14.3 (CH_3) 14.2 (CH_3). $C_{14}H_{21}NO_6$ (299.32). HRMS (ESI-FT-ICR): *m/z* = 322.12587; calcd. for $[C_{14}H_{21}NO_6Na]^+$: *m/z* = 322.12611.

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References

1. Hughes, A. B., Ed. *Amino Acids, Peptides and Proteins in Organic Chemistry* Wiley-VCH: Weinheim, 2009.
2. Royo Gracia, S.; Gaus, K.; Sewald, N. *Future Med. Chem.* **2009**, *1*, 1289.

3. Sonawane, V. C. *Crit. Rev. Biotechnol.* **2006**, *26*, 95.
4. Couty, F. *Amino Acids* **1999**, *16*, 297.
5. Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc*. **1990**, *112*, 5583.
6. Gatto, G. J., Jr.; Boyne, M. T., 2nd; Kelleher, N. L.; Walsh, C. T. *J. Am. Chem. Soc.* **2006**, *128*, 3838.
7. Germann, U. A.; Shlyakhter, D.; Mason, V. S.; Zelle, R. E.; Duffy, J. P.; Galullo, V.; Armistead, D. M.; Saunders, J. O.; Boger, J.; Harding, M. W. *Anticancer Drugs* **1997**, *8*, 125.
8. Boger, D. L.; Chen, J.-H.; Saionz, K. W. *J. Am. Chem. Soc.* **1996**, *118*, 1629.
9. Fujii, T.; Mukaihara, M.; Agematu, H.; Tsunekawa, H. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 622.
10. Singh, S. B.; Zink, D. L.; Liesch, J. M.; Mosley, R. T.; Dombrowski, A. W.; Bills, G. F.; Darkin-Rattray, S. J.; Schmatz, D. M.; Goetz, M. A. *J. Org. Chem.* **2002**, *67*, 815.
11. Bieliauskas, A. V.; Pflum, M. K. H. *Chem. Soc. Rev.* **2008**, *37*, 1402.
12. Zhang, X.; Chen, D.; Liu, X.; Feng, X. *J. Org. Chem*. **2007**, *72*, 5227.
13. Cowell, S. M.; Lee, Y. S.; Cain, J.P.; Hruby, V. J. *Curr. Med. Chem*. **2004**, *11*, 2785.
14. Kadouri-Puchot, C.; Comesse, S. *Amino Acids*, **2005**, *29*, 101.
15. Claesen, M.; Vlietinck, A.; Vanderhaeghe, H. *Bull. Soc. Chim. Belg.* **1968**, *77*, 587.
16. Baldwin, J. E.; Herchen, S. R.; Johnson, B. L.; Jung, M.; Usher, J. J.; Wan, T. *J. Chem. Soc., Perkin Trans. I* **1981,** 2253.
17. Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5043.
18. Huang, S.-B.; Nelson, J. S.; Weller, D. D. *Synth. Commun.* **1989**, *19*, 3485.
19. Pabba, J.; Mohal, N.; Vasella, A. *Helv. Chim. Acta*, **2006,** *89*, 1373.
20. Watanabe, L. A.; Haranaka, S.; Jose, B.; Yoshida, M.; Kato, T.; Moriguchi, M.; Soda, K.; Nishino N. *Tetrahedron: Asymm*. **2005,** *16*, 903.

