Concise, three-step enantioselective total synthesis of (4*S*,5*S*)-4-hydroxy-5-octylpyrrolidin-2-one, a colibactin pathway metabolite

Dong-Yang Shao and Pei-Qiang Huang*

*Department of Chemistry, Fujian Provincial Key Laboratory of Chemical Biology, College of Chemistry and
Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, P. R. China
E-mail: pqhuang@xmu.edu.cn*

**Dedicated with best wishes to Professor Tien-Yau Luh on the occasion of his 76th birthday**

Abstract

We report the first synthesis of (4*S*,5*S*)-4-hydroxy-5-octylpyrrolidin-2-one, one of the colibactin pathway metabolites isolated and characterized in 2021. Our synthesis started from (*S*)-malimide, a chiral building block previously developed from our laboratory. The first five-step approach consists of a highly regioselective Grignard addition at C-2 of (*S*)-malimide, catalytic dehydration, catalytic *cis*-selective hydrogenation of enamide, and successive cleavages of *N*-PMB and *O*-benzyl groups. By telescoping three reactions into one step, an even concise, three-step enantioselective total synthesis of the title compound has been achieved. Through this first enantioselective total synthesis, full physical and spectral data of this natural product were obtained.
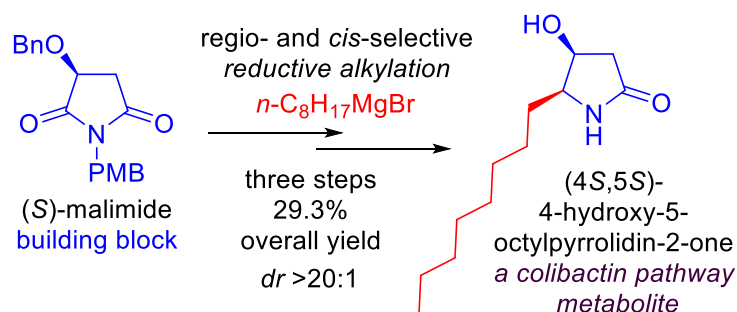
Keywords: γ-Lactam, natural products, stereoselective synthesis, asymmetric synthesis, malimide.

Introduction

Natural products have long been recognized as the most important resources for developing new medicines.[1] However, since the early 1990', with the emergence of novel technologies such as combinatory chemistry and high throughput screening (HTS), the natural product-based drug discovery strategy has been abandoned by the major pharmaceutical companies. About fifteen years late, although the renaissance of drug discovery from natural products has had been expected, it is challenging for several reasons. Among them, the availability of natural products and analogs remains the major challenge. Thus, the synthetic efficiency is becoming one of the major pursuits of total synthesis of natural products.[2]

Traditionally, natural products refer to secondary metabolites of plants, animals, and microorganisms,[1] which are considered to be the chemicals useful for their survival in the related ecological systems. Investigation of natural products from humans is rare. However, the investigation on steroids and prostaglandins have resulted in a series of important medicines in modern society. On the other hand, during recent decades, it has been recognized that the human microbiota is a dynamic collection of microbes that have existed within and on us, throughout our evolutionary history,[3] and microbe-derived natural products are mediators of many human disease.[4] Colibactins are a group of genotoxic secondary metabolites produced by some members of the gut microbiota, including *Escherichia coli* and other Enterobacteriaceae, which show genotoxicity relevant to colorectal cancer. In 2021, the teams of Kim and Crawford reported 10 new colibactin pathway metabolites (**1** - **10**). These compounds were revealed to be produced from a new biosynthetic cross-talk relationship between secondary polyketide and primary fatty acid pathways featuring an α-aminomalonate-derived lactam ring.[5] Among them the two most abundant metabolites were isolated and structurally characterized as (4*S*,5*S*)-5-octyl-4-hydroxypyrrolidin-2-one (**1**) and (4*S*,5*S*)-5-[(*Z*)-dec-3-en-1-yl]-4-hydroxypyrrolidin-2-one (**2**). Although the absolute configuration of natural lactam **1** has been determined as 4*S*,5*S*, its optical rotation has not been reported, neither biological activities, possibly due to the paucity of the natural product.

Although biological activities of γ-lactams **1** and **2** are unknown, γ-lactam is a structural motif found in a number of bioactive natural products and medicines, which display a wide range of bioactivities.[6-10] For example, streptopyrrolidine (**11**) was isolated as an angiogenesis inhibitor from the fermentation broth of a marine *Streptomyces* sp. isolated from the deep-sea sediment,[11] levetiracetam (**12**) is applied as a medication for epilepsy with a global sale of 770 M€ in 2018,[12] while (−)-clausenamide (**13**), a natural product isolated from traditional Chinese medicinal plant, is under clinical trial as a potential drug for treatment of Alzheimer's disease.[13]
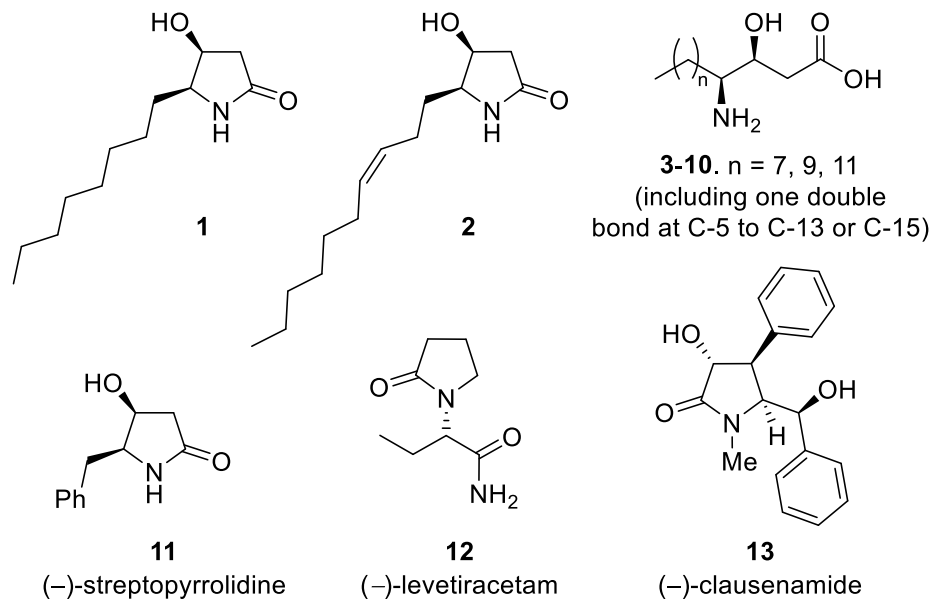
Figure 1. Representative γ-lactam-containing bioactive natural products and medicinal agents.

Our group has long been interested in the development of efficient synthetic methodologies[14-18] and concise total synthesis of natural products.[19-21] As a biomimetic approach,[2,22] we have developed several chiral building blocks and related selective reactions. One of such building block-based methodology is protected (*S*)-malimide (**4**)[23] and the regio- and *trans*-diastereoselective reductive alkylation. In 2009, the report of (−)-streptopyrrolidine (**11**) as a natural product[11] prompted us to develop a method for the *cis*-selective reductive alkylation of malimide and achieved the first total synthesis of this natural product.[23] We report herein the first enantioselective total synthesis of natural product **1**, which allowed revealing its optical rotation as levorotatory.

Results and Discussion

Because **1** is an analog of (−)-streptopyrrolidine (**11**), hence the synthetic route developed for the synthesis of **11**[23] was adopted. Thus, our synthesis started with Grignard addition (Scheme 1). Treatment of the known *N,O*-bis-protected (*S*)-malimide **14**[23] with *n*-octyl magnesium bromide in CH_2Cl_2 at −15 °C for 45 minutes yielded regioselectively (4*S*)-hemiaminal **15** as a diastereomeric mixture. Because the subsequent dehydration reaction was supposed to run through *N*-acyliminium intermediate **A**, the diastereomeric mixture, without separation, was subjected to the TsOH·H_2O-catalyzed (5 mol %) dehydration reaction (CH_2Cl_2, 0 °C to RT) to give enamide **16** in 62% yield over two steps. Compound **16** was obtained as the sole observable regio and (*E*)-geometric isomer. The latter was tentatively assigned by analogy with our previous results.[23] Subjecting enamide **16** to 10% Pd/C catalyzed hydrogenation in the presence of NH_4OAc afforded *N,O*-bis-protected hydroxylactam **17** as a single diastereomer (*dr* > 20:1, determined by ^{1}H NMR spectroscopy of the crude reaction products) in 73% yield. Exposing **17** to ceric ammonium nitrate (CAN) in a mixed solvent system [MeCN/H_2O = 9:1 (*v/v*)] allowed cleaving the *N*-protecting group (PMB) to give **18** in 85% yield. Finally, under 10% Pd/C-catalyzed hydrogenolysis conditions (H_2, 2 M HCl), **18** was debenzylated to produce the target molecule **1** in 92% yield {white solid, mp: 82 − 83 °C; $[\alpha]_D^{20}$ −31.3 (*c* 1.0, CHCl$_3$)}. Because our synthesis started from (*S*)-malimide **14**, the absolute configuration of our synthetic product is the natural one: (4*S*,5*S*)-**1**. The

spectral data of our synthetic compound **1** are identical with those reported for the natural product **1**. Thus, we have achieved a five-step total synthesis of natural γ-lactam (4*S*,5*S*)-**1** from the known chiral building block (*S*)-**14**, and revealed the sense of this natural product's optical rotation as levorotatory.
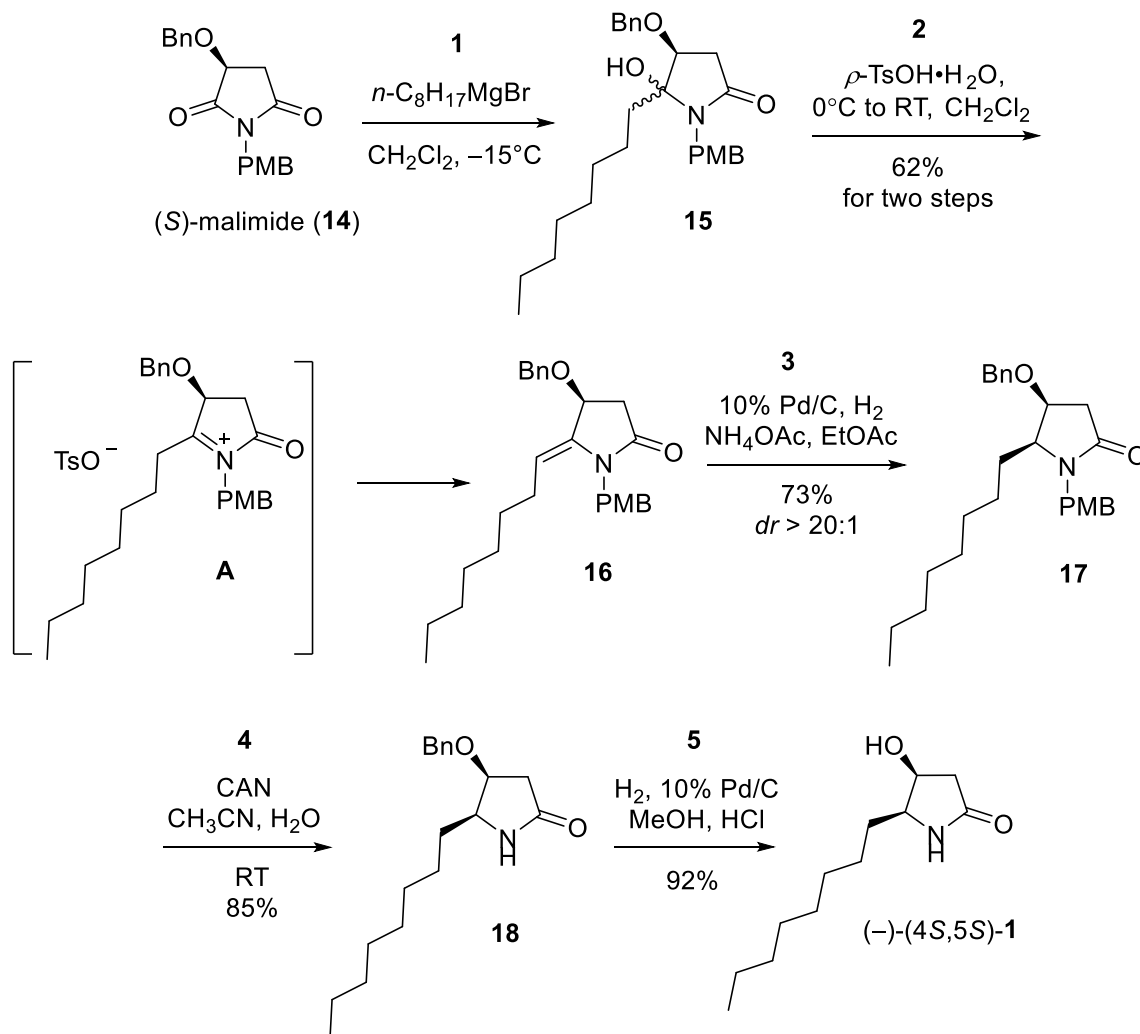
Scheme 1. Five-step enantioselective total synthesis of the title natural product.

To develop a more concise approach, telescoping the dehydration, hydrogenation, and *O*-debenzylation reactions was envisaged. As ceric ammonium nitrate be seen from Scheme 2, the modified approach also started with Grignard reagent addition with (*S*)-malimide **14**, which afforded C-2 addition product **15** as a mixture of two diastereomers in 73% yield. Next, the diastereomeric mixture **15** was treated with 5 mol % of TsOH·H₂O (CH₂Cl₂, 0 °C to RT). After removing the solvent, the residue was subjected to one-pot hydrogenation and hydrogenolysis (H₂, 10% Pd/C, NH₄OAc, MeOH, RT, 12 h; then *conc*. HCl, RT, 72 h) to afford β-hydroxy-γ-lactam **19** as a single diastereomer (*dr* > 20:1) in 46% yield from **15**. Finally, CAN-mediated *N*-deprotection of **19** produced (−)-(4*S*,5*S*)-**1** in 86% yield. Thus, we have achieved the three-step total synthesis of (−)-(4*S*,5*S*)-**1** with an overall yield of 29.3%.
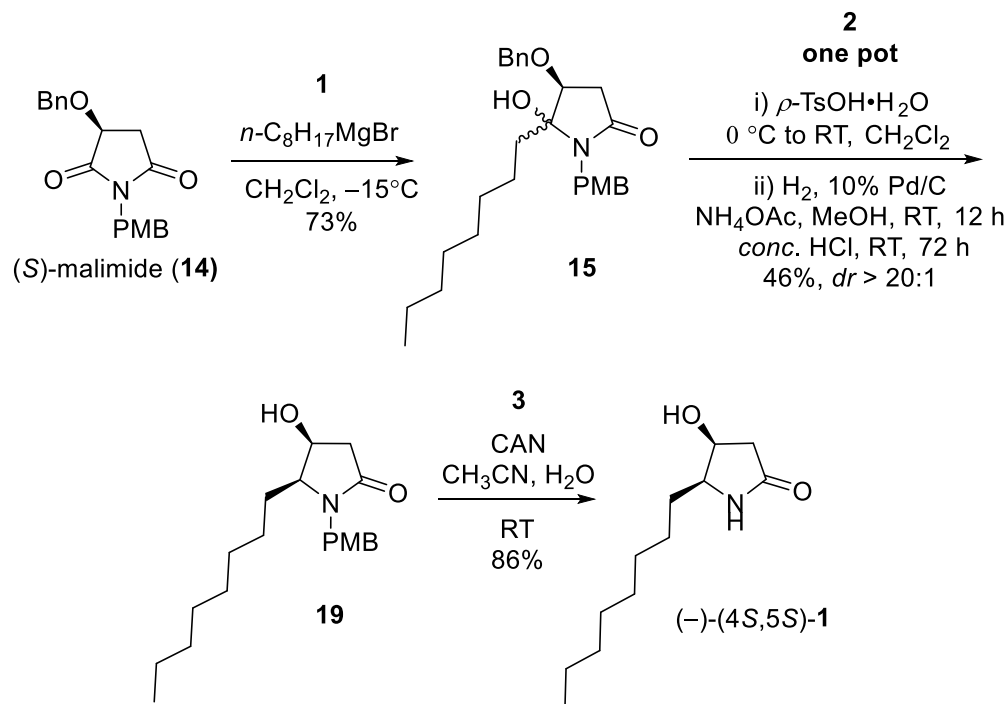
Scheme 2. Three-step enantioselective total synthesis of the title natural product.

Conclusions

To summarize, we have disclosed the first enantioselective total synthesis of (4*S*,5*S*)-4-hydroxy-5-octylpyrrolidin-2-one, achieved in five steps with an overall yield of 35.4% from the known chiral building block (*S*)-malimide (**14**). By telescoping three steps, a shorter, three-step total synthesis [five steps from commercially available (*S*)-malic acid] was accomplished with an overall yield of 29.3%. This work demonstrated once more the versatility of (*S*)-malimide for the enantioselective synthesis of functionalized, chiral γ-lactams which are ready precursors of other classes of natural products such as 2,5-disubstituted pyrrolidines[24-27] and γ-amino β-hydroxy carboxylic acids.[5] The work is ongoing in our laboratory, and results will be reported in due course.

Experimental Section

General. All commercially available reagents were used without further purification unless indicated otherwise. Column chromatography was performed on silica gel (300 - 400 mesh). Melting points were determined on a Büchi M560 Automatic Melting Point apparatus and are uncorrected. Optical rotation data were measured on an Anton Paar MCP 500 polarimeter at 589 nm. The information of chemical bonds or functional groups contained in the molecule were obtained by infrared spectroscopy on a Nicolet Avatar 330 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance III 400 with TMS as internal standard at room temperature. The samples were dissolved in $CDCl_3$ or DMSO-d_6. Chemical shifts were given in values of δ_H and δ_C referenced to residual solvent signals (δ_H 0.00 ppm for ^1H, δ_C 77.0 ppm for ^{13}C in $CDCl_3$, δ_H 2.50 ppm

for ^{1}H, δ_C 13.8 ppm for ^{13}C in DMSO-d_6). High resolution mass spectra (HRMS) were recorded using a Bruker Dalton Esquire 3000 plus mass spectrometer by the ESI method.

(S,E)-4-(Benzyloxy)-1-(4-methoxybenzyl)-5-octylidenepyrrolidin-2-one (16). To a solution of the known malimide **14**[23] (20 mmol, 6.51 g) in CH_2Cl_2 (150 mL) were slowly added *n*-octyl magnesium bromide (26 mmol, 1.3 equiv, 1 mol/L in THF) at −15 °C, the mixture was stirred at −15 °C for 45 min. The reaction was quenched with saturated NH_4Cl (20 mL), then the reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and filtered. After concentration under reduced pressure, the resulting residue without further purification required. To a solution of hemiaminal in dry CH_2Cl_2 (200 mL) was added 190 mg of *p*-TsOH·H_2O (1.0 mmol, 5 mol%) at 0 °C. The reaction mixture was stirred for 4 h at RT. The reaction was quenched with a saturated aqueous $NaHCO_3$ (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resultant residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:3) to give enamide **16** (5.23 g, two steps yield: 62%) as a pale-yellow oil. $[\alpha]_D^{20}$ +85.2 (*c* = 1.0, $CHCl_3$); IR (film) ṽ 1028, 1512, 1672, 1716, 2852, 2921 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.08 − 1.48 (m, 10H), 1.95 − 2.21 (m, 2H), 2.69 (dd, *J* = 2.1, 17.8 Hz, 1H), 2.78 (dd, *J* = 6.9, 17.8 Hz, 1H), 3.79 (s, 3H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.65 (s, 2H), 4.76 (dt, *J* = 2.1, 6.9 Hz, 1H), 4.89 (t, *J* = 7.6 Hz, 1H), 6.80 − 6.88 (m, 2H), 7.14 − 7.22 (m, 2H), 7.25 − 7.43 (m, 5H) ppm; ^{13}C NMR (101 MHz, chloroform-*d*) δ 14.0, 22.5, 26.7, 29.1, 30.2, 31.7, 36.5, 42.8, 55.1, 69.8, 70.2, 108.1, 113.8 (2 C), 127.9, 128.0 (2 C), 128.4 (5 C), 137.3, 138.7, 158.7, 172.9 ppm; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NOH^+$ [M+H$^+$]: 422.2690; found: 422.2685.

(4S,5S)-4-(Benzyloxy)-1-(4-methoxybenzyl)-5-octylpyrrolidin-2-one (17). To a mixture of ammonium acetate (10 mmol, 771 mg) and 10% Pd/C (20 w/w %) were added successively 25 mL of EtOAc and a solution of enamide **16** (5 mmol, 2.11 g) in 5 mL of EtOAc. The mixture was stirred under 1 atm of hydrogen for 4 h at RT. The mixture was filtered through celite. After concentration under reduced pressure, the residue was purified by flash chromatography on silica gel (EtOAc/ PE = 1:1) to give solely *cis*-diastereomers **17** in 73% yield as a white solid. Mp: 47 - 49 °C. $[\alpha]_D^{20}$ +6.5 (*c* = 1.0, $CHCl_3$); IR (film) ṽ 1174, 1246, 1456, 1512, 1693, 2853, 2925 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.15 − 1.35 (m, 12H), 1.50 − 1.66 (m, 1H), 1.67 − 1.85 (m, 1H), 2.52 (dd, *J* = 6.3, 16.8 Hz, 1H), 2.60 (dd, *J* = 4.6, 16.8 Hz, 1H), 3.43 − 3.51 (m, 1H), 3.77 (s, 3H), 3.88 (d, *J* = 15.0 Hz, 1H), 3.99 − 4.17 (m, 1H), 4.38 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.97 (d, *J* = 15.0 Hz, 1H), 6.77 − 6.87 (m, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.23 − 7.39 (m, 5H) ppm; ^{13}C NMR (101 MHz, chloroform-*d*) δ 14.0, 22.5, 25.1, 26.7, 29.1, 29.3, 29.7, 31.7, 37.0, 43.3, 55.1, 60.3, 71.2, 72.8, 113.9 (2 C), 127.5 (2 C), 127.7, 128.3 (2 C), 128.6, 129.1 (2 C), 137.6, 158.8, 172.6 ppm; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NOH^+$ [M+H$^+$]: 424.2846; found: 424.2842.

(4S,5S)-4-(Benzyloxy)-5-octylpyrrolidin-2-one (18). To a solution of compound **17** (2 mmol, 847 mg) in CH_3CN (60 mL) and H_2O (6.7 mL) was added ceric ammonium nitrate (10 mmol, 5.30 g), and the mixture was stirred at room temperature for 4 h. To the resulting mixture was added H_2O (60 mL), and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed successively with saturated aqueous sodium bicarbonate and brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. After concentration under reduced pressure, the resulting residue was purified by flash chromatography on silica gel (EtOAc/ PE = 2:1) to give compound **18** (515 mg, 85%) as a white solid. Mp: 88 - 89 °C. $[\alpha]_D^{20}$ −39.7 (*c* = 1.28, $CHCl_3$); IR (film) ṽ 835, 857, 1275, 1346, 1455, 1684, 1733, 2851, 2884, 2924, 2946, 3250 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.12 − 1.47 (m, 12H), 1.48 − 1.64 (m, 1H), 1.64 − 1.83 (m, 1H), 2.48 (d, *J* = 5.4 Hz, 2H), 3.61 − 3.79 (m, 1H), 4.10 − 4.25 (m, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 6.84 (d, *J* = 8.1 Hz,

1H), 7.15 – 7.50 (m, 5H) ppm; ^{13}C NMR (101 MHz, chloroform-*d*) δ 14.1, 22.6, 26.0, 29.2 (2 C), 29.4, 29.6, 31.8, 36.8, 58.5, 71.3, 75.1, 127.6 (2 C), 127.8, 128.4 (2 C), 137.6, 175.5 ppm; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NOH^+$ [M+H$^+$]: 304.2271; found: 304.2268.

(4*S*,5*S*)-4-Hydroxy-5-octylpyrrolidin-2-one (1). To 151 mg of 10% Pd/C was added a solution of compound **18** (303 mg, 1 mmol) in 20 mL of methanol. Then 2 - 3 drops of HCl (2 m) were added into the mixture. The mixture was stirred under 1 atm of hydrogen for 96 h at RT. It was filtered through celite. After concentration under reduced pressure, the resulting residue was purified by flash chromatography on silica gel (DCM/ MeOH = 20:1) to give (−)-(4*S*,5*S*)-**1** (197 mg, 92%) as a white solid. Mp: 82 - 83 °C. [α]$_D^{20}$ −31.3 (*c* = 0.5, CHCl$_3$); IR (film) ṽ 1008, 1027, 1054, 1689, 2125, 2251, 2854, 2925, 3443 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.17 – 1.29 (m, 11H), 1.29 – 1.39 (m, 2H), 1.46 − 1.59 (m, 1H), 1.93 (dd, *J* = 2.7, 16.5 Hz, 1H), 2.38 (dd, *J* = 6.1, 16.5 Hz, 1H), 3.34 – 3.40 (m, 1H), 4.07 – 4.29 (m, 1H), 4.91 (d, *J* = 5.0 Hz, 1H), 7.59 (br s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 13.8, 21.9, 25.3, 28.5, 28.7, 28.8, 29.1, 31.2, 40.6, 58.6, 67.1, 174.8 ppm; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NOH^+$ [M+H$^+$]: 214.1802; found: 214.1802.

(*S*,*E*)-4-(Benzyloxy)-1-(4-methoxybenzyl)-5-octylidenepyrrolidin-2-one (15). To a solution of malimide derivatives **14** (20 mmol, 6.51 g) in CH$_2$Cl$_2$ (150 mL) was slowly added *n*-octyl magnesium bromide (26 mmol, 1.3 equiv, 1 mol/L in THF) at −15 °C. The mixture was stirred at −15 °C for 45 min. The reaction was quenched with saturated NH$_4$Cl (20 mL), then the mixture was extracted with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na$_2$SO$_4$, and filtered. After concentration under reduced pressure, the resulting residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:1) to give enamide **15** (6.51 g, 74%) as a pale-yellow oil, diastereomeric mixture which was used in the next step without separation. A sample of pure major diastereomer was obtained from chromatographic separate. IR (film) ṽ 1035, 1071, 1136, 1176, 1247, 1347, 1409, 1455, 1514, 1613, 1673, 2854, 2926, 3361 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.00 − 1.31 (m, 11H), 1.34 − 1.48 (m, 1H), 1.66 − 1.87 (m, 2H), 1.93 (s, 1H), 2.42 (dd, *J* = 4.4, 16.9 Hz, 1H), 2.70 (dd, *J* = 6.7, 16.9 Hz, 1H), 3.75 (s, 3H), 3.92 (dd, *J* = 4.4, 6.6 Hz, 1H), 4.33 (d, *J* = 15.2 Hz, 1H), 4.43 – 4.53 (m, 2H), 4.59 (d, *J* = 11.8 Hz, 1H), 6.75 − 6.83 (m, 2H), 7.21 − 7.38 (m, 7H) ppm; ^{13}C NMR (101 MHz, chloroform-*d*) δ 14.0, 22.6, 23.2, 29.1, 29.3, 29.8, 31.8, 34.8, 35.8, 41.6, 55.2, 71.7, 80.0, 94.6, 113.9 (2 C), 127.6 (2 C), 127.8, 128.4 (2 C), 129.4 (2 C), 130.3, 137.5, 158.8, 172.8 ppm; HRMS (ESI) *m/z* calcd for $C_{27}H_{37}NO_4H^+$ [M+H$^+$]: 440.2796; found: 440.2792.

(4*S*,5*S*)-4-Hydroxy-1-(4-methoxybenzyl)-5-octylpyrrolidin-2-one (19). To a solution of hemiaminal **15** (2 mmol, 880 mg) in dry CH$_2$Cl$_2$ (10 mL) was added 75 mg of TsOH·H$_2$O (0.1 mmol, 19 mg) at 0 °C. The reaction mixture was stirred for 2 h at RT, concentrated under reduced pressure. To a mixture of the resultant residue, ammonium acetate (4 mmol, 308 mg) and 10% Pd/C (50 w/w %) were added successively 5 mL of MeOH. The mixture was stirred under 1 atm of hydrogen for 12 h at RT. Then 2 - 3 drops of *conc*. HCl were added into the mixture. The mixture was stirred under 1 atm of hydrogen for 72 h at RT. It was filtered through celite. After concentration under reduced pressure, the resulting residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:1) to give **19** (306 mg, 46%) as a white solid. Mp: 92 − 93 °C. [α]$_D^{25}$ −20.3 (*c* = 1.15, CHCl$_3$); IR (film) ṽ 843, 910, 1035, 1247, 1515, 1540, 1648, 2851, 2927, 3450 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.24 (s, 11H), 1.40 (tt, *J* = 6.5, 13.8 Hz, 1H), 1.65 (q, *J* = 7.4 Hz, 2H), 1.86 (s, 1H), 2.46 (dd, *J* = 2.5, 17.2 Hz, 1H), 2.64 (dd, *J* = 6.0, 17.2 Hz, 1H), 3.31 − 3.42 (m, 1H), 3.79 (s, 3H), 3.90 (dd, *J* = 3.2, 15.0 Hz, 1H), 4.23 − 4.39 (m, 1H), 4.94 (d, *J* = 15.0 Hz, 1H), 6.79 − 6.91 (m, 2H), 7.10 − 7.16 (m, 2H) ppm; ^{13}C NMR (101 MHz, chloroform-*d*) δ 14.1, 22.6, 25.2, 26.5, 29.2, 29.4, 29.7, 31.8, 41.0, 43.2, 55.2, 61.6, 66.2, 114.0 (2 C), 128.6, 129.0 (2 C), 158.9, 173.5 ppm; HRMS (ESI) *m/z* calcd for $C_{20}H_{31}NO_3H^+$ [M+H$^+$]: 214.1802; found: 214.1802.

(4*S*,5*S*)-4-Hydroxy-5-octylpyrrolidin-2-one (1). To a solution of compound **19** (1 mmol, 333 mg) in CH$_3$CN (5.4 mL) and H$_2$O (0.6 mL) was added ceric ammonium nitrate (5 mmol, 2.65 g), and the mixture was stirred at room temperature for 6 h. To the resulting mixture was added H$_2$O (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed successively with saturated aqueous sodium bicarbonate and brine (5 mL), dried over anhydrous Na$_2$SO$_4$, and filtered. After concentration under reduced pressure, the resulting residue was purified by flash chromatography on silica gel (DCM/MeOH = 20:1) to give compound (−)-(4*S*,5*S*)-**1** (184 mg, 86%) as a white solid. All data are in agreement with those of the product synthesized from **18**.

Acknowledgements

Supplementary Material

^{1}H and ^{13}C NMR spectra of compounds **1**, **15 – 19.**

References

1. Newman, D. J.; Cragg, G. M. *J. Nat. Prod*. **2020**, *83*, 770–803.
   https://doi.org/10.1021/acs.jnatprod.9b01285
2. Huang, P.-Q.; Yao, Z.-J.; Hsung, R. P. Efficiency in Natural Product Total Synthesis, Wiley, Hoboken, **2018**.
   https:// doi/book/10.1002/9781118940228
3. Mousa, W. K.; Athar, B.; Merwin, N. J.; Magarvey, N. A. *Nat. Prod. Rep.* **2017**, *34*, 1302–1331.
   https://doi.org/10.1039/C7NP00021A
4. Garg, N.; Luzzatto-Knaan, T.; Melnik, A. V.; Caraballo-Rodríguez, A. M.; Floros, D. J.; Petras, D.; Gregor, R.; Dorrestein, P. C.; Phelan, V. V. *Nat. Prod. Rep.* **2017**, *34*, 194–219.
   https://doi.org/10.1039/C6NP00063K
5. Kim, C. S.; Turocy, T.; Moon, G.; Shine, E. E.; Crawford, J. M. *Org. Lett.* **2021**, *23*, 6895–6899.
   https://doi.org/10.1021/acs.orglett.1c02461
6. Caruano, J.; Muccioli, G.; Robiette, R. *Org. Biomol. Chem*. **2016**, *14*, 10134–10156.
   https://doi.org/10.1039/C6OB01349J
7. Zulkifli, M.; Pungot, N. H.; Abdullah, N.; Ash'ari, N. A. N.; Shaameri, Z. *Mini-Rev. Org. Chem.* **2022**, *19*, 681-685.
   https://dx.doi.org/10.2174/1570193X19666220110121158
8. Ahankar, H.; Ramazani, A.; Ślepokura K.; Kinzhybalo, V. *Arkivoc* **2022**, *iii*, 27-40*.*
   https://doi.org/10.24820/ark.5550190.p011.595
9. Wang, X.-D.; Shi, T.; Yin, G.-F.; Wang, Y.-Q.; Li, Z.; Wang, Z. *Org. Chem. Front.* **2022**, *9*, 3818-3822.
   https://doi.org/10.1039/D2QO00456A
10. Si, C. M.; Mao, Z. Y.; Liu, Y. W.; Du, Z. T. *Org. Chem. Front.* **2015**, *2*, 1485-1499.
    https://doi.org/10.1039/C5QO00250H

11. Shin, H. J.; Kim, T. S.; Lee, H.-S.; Park, J. Y.; Choi, I.-K.; Kwon, H. J. *Phytochemistry* **2008**, *69*, 2363-2366.
https://doi.org/10.1016/j.phytochem.2008.05.020

12. Arndt, S.; Grill, B.; Schwab, H.; Steinkellner, G.; Pogorevčnik, U.; Weis, D.; Nauth, A. M.; Gruber, K.; Opatz, T.; Donsbach, K.; Waldvogel, S. R.; Winkler, M. *Green Chem*. **2021**, *23*, 388-395.
https://doi.org/10.1039/D0GC03358H

13. Chu, S. F.; Zhang, J. T. *Acta Pharm. Sin. B* **2014**, *4*, 417-423.
https://doi.org/10.1016/j.apsb.2014.10.004

14. Han, F.; Lu, G.-S.; Wu, D. -P.; Huang, P.-Q. *Sci. China-Chem.* **2023**, *66*, 1094–1100.
https://doi.org/10.1007/s11426-022-1501-y

15. Chen, H.; Wu, Z.-Z.; Shao, D.-Y.; Huang, P.-Q. *Sci. Adv*. **2022**, *8*, eade3431.
https://www.science.org/doi/10.1126/sciadv.ade3431

16. Lu, H.-R.; Geng, H.; Ding, G.-T.; Huang, P.-Q. *Green Chem*. **2022**, *24*, 4405 – 4413.
https://doi.org/10.1039/D2GC00662F

17. Wang, X.-G.; Ou, W.; Liu, M.-H.; Liu, Z.-J.; Huang, P.-Q. *Org. Chem. Front.* **2022**, *9,* 3237 – 3246.
https://doi.org/10.1039/D2QO00335J

18. Chen, D.-H.; Sun, W.-T.; Zhu, C.-J.; Lu, G.-S.; Wu, D.-P.; Wang, A.-E; Huang, P.-Q. *Angew. Chem. Int. Ed.* **2021**, *60*, 8827 – 8831.
https://doi.org/10.1002/anie.202015898

19. Huang, Y.-H.; Liu, Z.-J.; Huang, P.-Q. *Org. Chem. Front.* **2022**, *9*, 58-63.
https://doi.org/10.1039/D1QO01408K

20. Hu, X.-N.; Wu, D.-P.; Xu, Y.-P.; Huang, P.-Q. *Chem. Eur. J.* **2021**, *27*, 609-613.
https://doi.org/10.1002/chem.202004261

21. Huang, X.-Z.; Gao, L.-H.; Huang, P.-Q. *Nat. Commun.* **2020**, *11*: 5314
https://doi.org/10.1038/s41467-020-19163-4

22. Luo, S-P.; Huang, P.-Q. *Prog. Chem.* **2020**, *32*, 1846-1868.
https://kns.cnki.net/kcms/detail/11.3383.o6.20201103.1632.024.html

23. Xiang, S.-H.; Yuan, H.-Q.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2009**, *20*, 2021-2026.
https://doi.org/10.1016/j.tetasy.2009.08.018

24. Feng, Y.-M.; Liu, C.-H.; Li, X.; Sun, J.-T.; Liu, N.-X.; Wei, B.-G. *Eur. J. Org. Chem*. **2023**, *26*, e202201331.
https://doi.org/10.1002/ejoc.202201331

25. Hausherr, A.; Siemeister, G.; Reissig, H.-U. *Org. Biomol. Chem.* **2019**, *17*, 122-134.
https://doi.org/10.1039/C8OB02645A

26. Si, C-M.; Shao, L-P.; Mao, Z-Y.; Zhou, W.; Wei, B.-G**.** *Org. Biomol. Chem*. **2017**, *15*, 649-661.
https://doi.org/10.1039/C6OB02523D

27. Buchman, M.; Csatayova, K.; Davies, S. G.; Fletcher, A. M.; Houlsby, I. T. T.; Roberts, P. M.; Rowe, S. M.; Thomson, J. E. *J. Org. Chem.* **2016**, *81*, 4907–4922.
https://doi.org/10.1039/C6OB02523D