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A novel approach to the Geissman–Waiss lactone and a key intermediate in the synthesis of pyrrolidine *trans*-lactones

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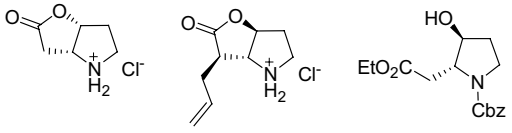
Abstract—Based on the highly regio- and diastereoselective reductive-ethoxycarbonylmethylation of protected (*S*)-malimide **4**, a new approach to the Geissman–Waiss lactone **1** and a key intermediate **3** for the synthesis of pyrrolidine *trans*-lactones (e.g., **2**) is described. The synthesis features a one-step and a two-step chemoselective reduction of an amide carbonyl in the presence of an ester group as the key steps.

1. Introduction

Pyrrolizidine alkaloids consisting of hydroxylated 1-methylpyrrolizidines (necine bases) and acidic moieties (necine acids) are widely present in plants.[1] Their diverse structures and interesting bioactivities, such as antitumor activity and carcinogenicity,[2] have attracted much synthetic attention. Particular attention has been paid to the synthesis of the pyrrolizidine moieties.[3]

Since the pioneering use of lactone **1** by Geissman and Waiss[4] as a key intermediate for the synthesis of (+)-retronecine,[4,5] this lactone (latterly known as Geissman–Waiss lactone) and its *N*-protected derivatives have become the standard intermediates for the synthesis of other necine bases, such as (−)-turneforcidine,[6] (+)-platynecine,[7] and (+)-croalbinecine.[5b] As a result, a number of approaches to enantioenriched Geissman–Waiss lactone have been reported.[8] In addition, structurally related pyrrolidine *trans*-lactone **2**,[9] prepared from **3**, has recently been introduced as a scaffold for designing inhibitors of serine proteases with the aim of developing therapies for respiratory and cardiovascular diseases amongst others. In connection with our work on the development of (*S*)-malimide-based synthetic methodology for the synthesis of bioactive pyrrolidines,[10] we report herein a new approach to (−)-Geissman–Waiss lactone **1** and pyrrolidine **3**, a key intermediate for the asymmetric synthesis of pyrrolidine *trans*-lactone **2** and swainsonine.



1 **2** **3**

2. Results and discussion

Central to our plan was the introduction of the side chain of Geissman–Waiss lactone via reductive alkylation of the protected (*S*)-malimide **4**[10c,f] in a regio- and diastereoselective manner. Although it has been observed that addition of alkyllithium reagents to malimide **4** leads to poor regioselectivity,[10f,11] in light of our recent results,[10g] we envisioned that ethyl acetate lithium enolate, being a stabilized organolithium reagent would behave similarly to Grignard reagents, leading to high C-2 regioselectivity. This turned out to be correct, when a THF solution of the known (*S*)-malimide **4**[10c,f] was added to a solution of lithium enolates, generated in situ from ethyl acetate at −78 °C, a pair of diastereomers **5** was obtained in 89% yield (based on the recovered starting material, **4**, 13%) (Scheme 1). No other regioisomers were detected after the subsequent reductive deoxygenation reaction. The observed high

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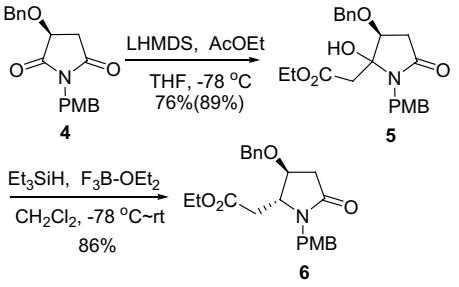
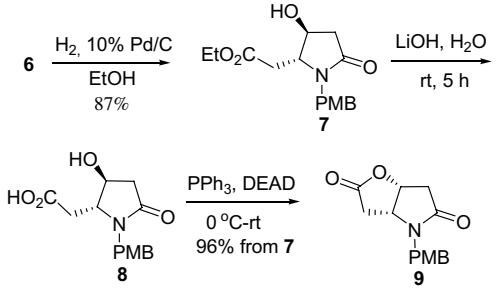


Scheme 1.

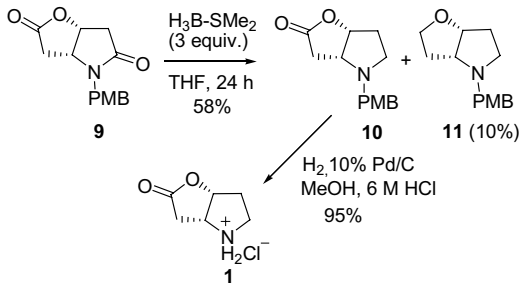
regioselectivity is in support of our previous argument that the different regioselective behaviors of Grignard reagents and alkyllithium vis-à-vis the (*S*)-malimide **4** was due to the higher reactivity of organolithium reagents, which precluded a precoordination of the metal ion (Li^+) with the oxygen atom at the C-3 position, while Grignard reagents did precoordinate, leading regioselectively to C-2 addition.[10f] Treatment of the diastereomeric *N*,*O*-acetal **5** with $F_3B{\cdot}OEt_2/Et_3SiH$[10,12] (−78 °C, then rt) led to the desired lactam **6**, as the only isolable diastereomer, in 86% yield. The stereochemistry of lactam **6** was assigned as *trans* according to the observed small vicinal coupling constants[10,13] ($J_{4,5} \approx 0$ Hz), which was further confirmed by converting **6** to known **1** and **3**.

Debenzylation of **6** under hydrogenolytic conditions (1 atm H_2, 10% Pd/C, EtOH, rt) provided hydroxy lactam **7** in 87% yield (Scheme 2). Compound **7** was then subjected successively to saponification (1.1 equiv LiOH, H_2O, rt, 5 h) and intramolecular Mitsunobu reaction conditions (PPh_3, DEAD, CH_2Cl_2, 0 °C–rt),[14] which afforded the desired lactone **9** in an overall yield of 96% from **7**.



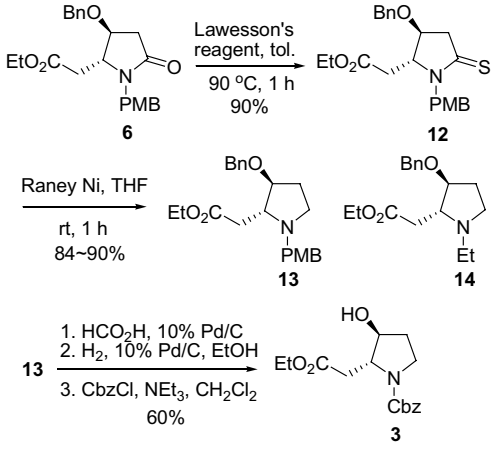
Scheme 2.

The next problem was the selective conversion of **9** to pyrrolidine *cis*-lactone **10**. Although a three-step procedure (thionation, ethylation with $Et_3O{\cdot}BF_4$ and selective reduction with $NaBH_3CN$)[5c,8h,i] has been developed for the selective deoxygenative reduction of the carbonyl of a lactone–lactam, a direct one-pot chemoselective reduction was desirable. A survey of the literature showed that the chemoselective reduction of an amide carbonyl in the presence of an ester group was possible.[15] However, selective reduction of an amide carbonyl without affecting the more reactive lactone carbonyl was a more difficult task. After several trials, it was observed that the chemoselective deoxygenation reduction of **9** could be achieved by treating **9** with 3 mol equiv of borane dimethylsulfide in THF at rt for 24 h. In such a way, the desired *cis*-pyrrolidine lactone **10** was obtained in about 58% yield. Furthermore, fully reduced **11** was isolated as a by-product in 10% yield (Scheme 3). To complete the synthesis of **1**, **10** was subjected to hydrogenolytic conditions (H_2, 10% Pd/C, 6 M HCl, MeOH) to provide Geissman–Waiss lactone **1**, which was isolated as the hydrochloride salt {mp 185–189 °C (EtOH/Et_2O), $[\alpha]_D^{20} = +45.0$ (*c* 0.4, MeOH); lit.[8h] mp 185–188 °C, $[\alpha]_D^{20} = +47.9$ (*c* 1.5, MeOH); lit.[5b] $[\alpha]_D^{20} = +45.6$ (*c* 0.3, MeOH)} in 95% yield.



Scheme 3.

Next, we turned our attention to the synthesis of protected 3-pyrrolidininol derivative **3**, the key intermediate for the synthesis of pyrrolidine *trans*-lactone **2**.[9] For this purpose, lactam–ester **6** was treated with borane dimethylsulfide in the same way as described for **9**. Unfortunately, the desired **13** was obtained, in the best case, in only 41% yield. We then decided to explore a two-step procedure[16] (Scheme 4). Thus, **6** was first treated with 2,4-bis(4-methoxyphenyl)-l,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent)[17] (90 °C, 1 h), which led to thioamide **12** in 90% yield. Subsequent desulfurization of **12** with Raney-nickel deserves comments. Initially, when **12** was treated with ethanol–washed Raney nickel (W-2), a large amount of C–N bond



Scheme 4.

cleaved/re-ethylated side product **14** was isolated. Such a side reaction has previously been observed.[18] After several trials, we found that when THF–washed Raney nickel (W-2) was used (rt, 1 h) instead, **13** could be obtained in high yields (84–90%).

Finally, successive *N*-debenzylation and *O*-debenzylation via transfer hydrogenolysis and catalytic hydrogenolysis led to the desired 3-pyrrolidinol derivative, which without further purification, was reprotected (CbzCl, NEt_3, CH_2Cl_2, rt) to give **3**[19] $\{[\alpha]_D^{20} = -33.9\}$ in 60% overall yield from **13**. It should be noted that transfer hydrogenolysis should be followed by catalytic hydrogenolysis so as to ensure the complete cleavage of both *N*,*O*-protective groups. Since compound **6** is a common intermediate in the syntheses of Geissman–Waiss lactone **1** and **3**, and no epimerization has been observed during the transformation from **6** to **3**, the enantiomeric excess of **3** was estimated to be 98% by comparing with that of Geissman–Waiss lactone **1**.

3. Conclusion

In conclusion, we have shown that ethyl acetate lithium enolates, being a moderate nucleophile, can add regioselectively at the C-2 carbonyl of the *N*,*O*-di-protected (*S*)-malimide **4** in excellent regioselectivity. A one-step and a two-step chemoselective amide carbonyl reduction procedure have been used respectively for the conversion of **6** to Geissman–Waiss lactone (+)-**1** and (−)-**3**. Since racemic **3** has been converted to (±)-**2**, our approach to enantioenriched **3** would, a priori, open a route to optically active **2**.

4. Experimental

4.1. General

All melting points were determined on a Yanaco MP-500 micro melting point apparatus and are uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian unity +500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by a Bruker Dalton ESquire 3000 plus liquid chromatography-mass spectrum (direct injection). Optical rotations were measured with a Perkin–Elmer 341 automatic polarimeter. Flash column chromatography was carried out with silica gel (200–300 mesh). Solvent THF was distilled over sodium, with dichloromethane being distilled over P_2O_5.

4.2. Ethyl (4*S*,5*R*)-[4-benzyloxy-1-(4-methoxybenzyl)-2-oxopyrrolidin-5-yl]acetate 6

To a solution of hexamethyldisilazane (0.33 mL, 1.34 mmol) in THF (1 mL) was added dropwise *n*-butyllithium (0.49 mL, 1.22 mmol) at −78 °C under N_2 atmosphere. After being stirred for 0.5 h, ethyl acetate (0.12 mL, 1.22 mmol) was added dropwise over 15 min and the stirring continued for another 15 min. To the ethyl lithioacetate was added dropwise a solution of **4** (394 mg, 1.22 mmol) in tetrahydrofuran (0.6 mL) over 15 min and the stirring continued at −78 °C for 3 h. The reaction was quenched by the addition of hydrochloric acid (2 M, 1 mL). The cooling bath was removed, and the solution allowed to warm to room temperature. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 2 mL). The combined extracts were washed successively with a saturated solution of $NaHCO_3$ and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Flash chromatographic purification (eluent: AcOEt–PE = 1:2) of the crude afforded **5** (white solid, 381 mg, diastereomeric mixture, combined yield: 76%) and the recovered starting material **4** (53 mg, 13%). Carbinol **5** was used in the next step as a diastereomeric mixture.

To a cooled (−78 °C) solution of the diastereomeric mixture **5** (970 mg, 2.34 mmol) in dichloromethane (14 mL) was added successively Et_3SiH (3.73 mL, 23.4 mmol) and $BF_3{\cdot}OEt_2$ (0.88 mL, 7.0 mmol) under an N_2 atmosphere. The resulting mixture was stirred at −78 °C for 6 h and at room temperature overnight. The resultant mixture was quenched by addition of a saturated solution of $NaHCO_3$ at 0 °C. After the mixture was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatographic purification of the crude (eluent: EtOAc–PE = 1:2) afforded **6** (822 mg, 86%) as a pale yellow oil. $[\alpha]_D^{20} = +24.5$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3031, 2931, 1731, 1693, 1513, 1247, 1177, 1029 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 2.32 (dd, *J* = 8.7, 15.8 Hz, 1H, CH_2COO), 2.52 (d, *J* = 17.4 Hz, 1H, H-3), 2.56 (dd, *J* = 3.9, 15.8 Hz, 1H, CH_2COO), 2.77 (dd, *J* = 6.2, 17.4 Hz, 1H, H-3), 3.79 (s, 3H, OCH_3), 3.89 (dd, *J* = 3.9, 8.7 Hz, 1H, H-5), 3.99 (m, 1H, H-4), 4.00 (d, *J* = 15.0 Hz, 1H, NCH_2Ar), 4.10 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 4.46 (d, *J* = 11.8 Hz, 1H, OCH_2Ph), 4.50 (d, *J* = 11.8 Hz, 1H, OCH_2Ph), 4.89 (d, *J* = 15.0 Hz, 1H, NCH_2Ar), 6.80–7.38 (m, 9H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1 (CH_2CH_3), 35.6 (CH_2COO), 37.2 (C-3), 43.7 (C-5), 55.3 (NCH_2Ar), 59.9, 61.0 (CH_2CH_3), 70.6, 75.9 (OCH_2Ph), 114.1, 127.7, 127.8, 128.1, 128.4, 129.1, 137.6, 159.1 (Ar), 170.2 (C-2), 172.8 (*C*OO) ppm. MS (ESI, *m*/*z*): 420 ($M+Na^+$, 40), 398 ($M+H^+$, 100). HRMS calcd for $[C_{23}H_{27}NO_5+H]^+$: 398.1962. Found: 398.1961.

4.3. Ethyl (4*S*,5*R*)-[4-hydroxy-1-(4-methoxybenzyl)-2-oxopyrrolidin-5-yl]acetate 7

A mixture of **6** (225 mg, 0.57 mmol) and 10% Pd/C (56 mg) in EtOH (3 mL) was stirred under an atmosphere of hydrogen (1 atm, balloon technique) at room temperature for 9 days. The catalyst was filtered through Celite, and the filtrate washed successively with a saturated solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under

reduced pressure. Column chromatographic purification of the crude (eluent: EtOAc–PE = 2.5:1) afforded **7** as colorless crystals (152 mg, 87%). Mp 50–52 °C (EtOAc/PE). $[\alpha]_D^{20} = +1.6$ (*c* 1.1, $CHCl_3$). IR (film) ν_{max}: 3379, 2933, 1730, 1670, 1514, 1247, 1177, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 2.31 (dd, $J = 9.6$, 16.5 Hz, 1H, CH_2COO), 2.44 (dd, $J = 3.5$, 17.6 Hz, 1H, H-3), 2.67 (dd, $J = 3.9$, 16.5 Hz, 1H, CH_2COO), 2.81 (dd, $J = 7.1$, 17.6 Hz, 1H, H-3), 3.63 (ddd, $J = 2.6$, 3.9, 9.6 Hz, 1H, H-5), 3.79 (s, 3H, OCH_3), 3.98 (d, $J = 15.2$ Hz, 1H, NCH_2Ar), 4.11 (q, $J = 7.1$ Hz, 2H, CH_2CH_3), 4.24 (m, 1H, H-4), 4.85 (d, $J = 15.2$ Hz, 1H, NH_2Ar), 6.80–7.30 (m, 4H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0 (CH_2CH_3), 36.1 (CH_2COO), 39.00 (C-3), 43.6 (C-5), 55.2 (NCH_2Ar), 61.3 (C-4), 62.5 (CH_2CH_3), 70.1 (OCH_3), 114.1, 127.84, 129.1, 159.1 (Ar), 171.2 (C-2), 172.6 (COO) ppm. MS (ESI, *m/z*): 330 ($M+Na^+$, 20), 308 ($M+H^+$, 100). HRMS calcd for $[C_{16}H_{21}NO_5+H]^+$: 308.1492. Found: 308.1491. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.33; H, 6.89; N, 4.65.

4.4. (4*S*,5*R*)-2-[4-Hydroxy-1-(4-methoxybenzyl)-2-oxopyrrolidin-5-yl]acetic acid 8

To a stirred solution of **7** (110 mg, 0.36 mmol) in EtOH (2.1 mL) was added 1 M aqueous LiOH (0.4 mL) at 0 °C. The solution was stirred at room temperature for 5 h, and then acidified with 6 M HCl to pH 2–3. After the mixture was extracted with CH_2Cl_2 (3 × 3 mL), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude **8**, which was used in the next step without further purification.

4.5. (1*R*,5*R*)-6-(4-Methoxybenzyl)-2-oxa-6-azabicyclo-[3.3.0]octan-3,7-dione 9

To a mixture of crude **8** and PPh_3 (113 mg, 0.43 mmol) in THF (3.6 mL) was added dropwise DEAD (0.07 mL, 0.43 mmol) at 0 °C. After being stirred at rt for 0.5 h, the mixture was concentrated under reduced pressure. Flash chromatographic purification of the crude (AcOEt–PE = 1:1.5–2:1) afforded **9** (90 mg, 96%) as a white solid. Mp 109–111 °C (EtOAc/PE). $[\alpha]_D^{20} = +48.2$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 2998, 2935, 2839, 1784, 1695, 1514, 1404, 1245, 1173, 1030 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.63 (dd, $J = 6.6$, 18.3 Hz, 1H, $NCOCH_2$), 2.70 (dd, $J = 1.2$, 18.3 Hz, 1H, $NCOCH_2$), 2.82 (m, 2H, CH_2COO), 3.80 (s, 3H, OCH_3), 3.96 (d, $J = 15.0$ Hz, 1H, NCH_2Ar), 4.18 (ddd, $J = 1.2$, 5.2, 6.6 Hz, 1H, CHN), 4.93 (d, $J = 15.0$ Hz, 1H, NCH_2Ar), 5.04 (ddd, $J = 2.9$, 5.2, 8.0 Hz, 1H, CHO), 6.82–7.30 (m, 4H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 32.6 (CHN), 37.1 ($NCOCH_2$), 44.0 (CH_2COO), 55.3 (NCH_2Ar), 57.2 (OMe), 75.5 (CHO), 114.4, 127.0, 129.5, 159.5 (Ar), 171.2 (NCO), 173.8 (COO) ppm. MS (ESI, *m/z*): 284 ($M+Na^+$, 60), 262 ($M+H^+$, 100). HRMS calcd for $[C_{14}H_{15}NO_4+H]^+$: 262.1074. Found: 262.1072. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.68; H, 5.91; N, 5.31.

4.6. (1*R*,5*R*)-6-(4-Methoxybenzyl)-2-oxa-6-azabicyclo-[3.3.0]octan-3-one 10

To a solution of **9** (60 mg, 0.23 mmol) in dry tetrahydrofuran (4.6 mL) was added dropwise borane dimethylsulfide complex (0.05 mL, 0.58 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred at 0 °C for 0.5 h and then at rt for 19 h. Methanol was added until the evolution of gas had ended. The solvents were removed under reduced pressure. Methanol (4 × 5 mL) was added and then evaporated (this procedure was repeated for four times). Purification of the residue by silica gel chromatography (AcOEt–PE = 1:2.5) afforded **10** (32 mg, 58%) as colorless crystals. Mp 59–61 °C (EtOAc/PE). $[\alpha]_D^{20} = -3.65$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 2929, 2836, 1774, 1611, 1512, 1248, 1163, 1093, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.04 (m, 1H, NCH_2CH_2), 2.24 (m, 1H, NCH_2CH_2), 2.31 (m, 1H, NCH_2), 2.48 (d, $J = 17.9$ Hz, 1H, CH_2COO), 2.55 (dd, $J = 6.5$, 17.9 Hz, 1H, CH_2COO), 3.02 (t, $J = 8.0$ Hz, 1H, NCH_2), 3.22 (s, 1H, CH N), 3.42 (d, $J = 12.7$ Hz, 1H, NCH_2Ar), 3.75 (d, $J = 12.7$ Hz, 1H, NCH_2Ar), 4.98 (m, 1H, CHO), 6.82–7.30 (m, 4H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.1 (NCH_2CH_2), 34.7 (CH_2COO), 52.3 (NCH_2), 55.2 (CHN), 57.1 (OCH_3), 63.3 (NCH_2Ar), 83.9 (CHO), 113.8, 129.9, 159.9 (Ar), 176.5 (COO) ppm. MS (ESI, *m/z*): 270 ($M+Na^+$, 10), 248 ($M+H^+$, 100). HRMS calcd for $[C_{14}H_{17}NO_3+H]^+$: 248.1281. Found: 248.1283.

4.7. (1*R*,5*R*)-2-Oxa-6-azabicyclo[3.3.0]octan-3-one hydrochloride 1

To a mixture of **10** (20 mg, 0.08 mmol) and 10% Pd–C (8 mg) were added successively methanol (0.5 mL) and 6 M hydrochloric acid (0.1 mL) at 0 °C. The mixture was stirred at room temperature under an atmosphere of H_2 overnight. The mixture was filtered through a Celite pad and then evaporated to give a yellow solid, which was triturated with ethanol and recrystallized to provide lactone **1** as a white solid (11 mg, 95%). Mp 185–189 °C ($EtOH/Et_2O$) (lit.[5b,8n] mp 182–184 °C; lit.[8g] mp 185–186 °C). $[\alpha]_D^{20} = +45.0$ (*c* 0.4, MeOH) {lit.[5b,8n] $[\alpha]_D^{20} = +45.6$ (*c* 0.3, MeOH); lit.[8g] $[\alpha]_D^{20} = +45.8$ (*c* 0.56, MeOH)}. IR (film) ν_{max}: 3388, 2924, 1777, 1719, 1442 cm^{-1}. ^1H NMR (500 MHz, D_2O): δ 2.34–2.44 (m, 1H, NCH_2CH_2), 2.47–2.54 (m, 1H, NCH_2CH_2), 3.03 (dd, $J = 1.6$, 19.7 Hz, 1H, CH_2COO), 3.32 (dd, $J = 8.8$, 19.7 Hz, 1H, CH_2COO), 3.48 (ddd, $J = 6.6$, 11.1, 12.0 Hz, 1H, NCH_2), 3.59 (ddd, $J = 3.4$, 7.8, 12.0 Hz, 1H, NCH_2), 4.71 (ddd, $J = 1.6$, 5.7, 8.8 Hz, 1H, CHN), 5.45 (ddd, $J = 0.9$, 5.4, 5.7 Hz, 1H, CHO) ppm. ^{13}C NMR (125 MHz, D_2O): δ 33.3 (NCH_2CH_2), 35.6 (NCH_2), 47.0 (CH_2COO), 61.8 (NCH), 86.5 (CHO), 179.9 (COO) ppm.

4.8. Ethyl (4*S*,5*R*)-[4-(benzyloxy)-1-(4-methoxybenzyl)-2-thioxopyrrolidin-5-yl]acetate 12

To a stirred solution of 282 mg (0.710 mmol) of **6** in dry toluene (28 mL) was added Lawesson's reagent (185 mg, 0.46 mmol) in one portion under N_2 atmosphere. The mixture was heated at 90 °C for 1 h. The resultant

mixture was cooled and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: ether–PE = 0.8:1) to give **12** (268 mg, 90%) as a white solid. Mp 88–90 °C (ether–PE). $[\alpha]_D^{20} = +99.5$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3029, 2978, 2930, 1731, 1612, 1585, 1513, 1482, 1248, 1178, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.14 (t, 3H, J = 7.2 Hz, CH_2CH_3), 2.28 (dd, J = 9.5, 16.2 Hz, 1H, CH_2COO), 2.51 (dd, J = 3.9, 16.2 Hz, 1H, CH_2COO), 3.12 (d, J = 18.5 Hz, 1H, H-3), 3.19 (dd, J = 5.4, 18.5 Hz, 1H, H-3), 3.70 (s, 3H, OCH_3), 3.90 (d, J = 5.4 Hz, 1H, H-4), 4.02 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.12 (dd, J = 3.9, 9.5 Hz, 1H, H-5), 4.22 (d, J = 14.9 Hz, 1H, NCH_2Ar), 4.34 (d, J = 12.4 Hz, 1H, OCH_2Ph), 4.36 (d, J = 12.4 Hz, 1H, OCH_2Ph), 5.56 (d, J = 14.9 Hz, 1H, NCH_2Ar), 6.70–7.28 (m, 9H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0 (CH_2CH_3), 34.6 (CH_2COO), 48.6 (C-3), 49.8 (C-4), 55.2 (NCH_2Ar), 61.2 (CH_2CH_3), 66.6 (OCH_3), 70.4 (CH_2Ph), 114.2, 126.6, 127.6, 127.7, 128.3, 129.1, 137.3, 159.3 (Ar), 169.7 (*C*OO), 200.4 (*C*-2) ppm. MS (ESI, *m*/*z*): 436 ($M+Na^+$, 6), 414 ($M+H^+$, 100). HRESIMS calcd for $[C_{23}H_{27}NO_4S+H]^+$: 414.1733. Found 414.1727.

4.9. Ethyl (2*R*,3*S*)-[3-(benzyloxy)-1-(4-methoxybenzyl)-pyrrolidin-2-yl]acetate 13

To a stirred suspension of Raney nickel (4 mL in dry THF) was added a solution of **12** (122 mg, 0.295 mmol) in dry THF (15 mL). The reaction mixture was stirred at room temperature for 1 h, and then filtered through Celite and washed repeatedly with methanol. The filtrates were concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: EtOAc–PE = 1:3) to give **13** as a pale yellow oil (95 mg, yield: 84%). $[\alpha]_D^{20} = -19.4$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3030, 2977, 2934, 2834, 1732, 1612, 1585, 1512, 1454, 1246, 1173, 1098, 1067 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.14 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.69–1.84 (m, 2H, H-4), 2.35 (dd, J = 7.9, 14.5 Hz, 1H, CH_2COO), 2.38–2.42 (m, 1H, H-5), 2.45 (dd, J = 4.6, 14.5 Hz, 1H, CH_2COO), 2.72–2.78 (m, 1H, H-5), 2.92–2.97 (m, 1H, H-2), 3.29 (d, J = 12.8 Hz, 1H, NCH_2Ar), 3.70 (s, 3H, OCH_3), 3.84 (d, J = 12.8 Hz, 1H, NCH_2Ar), 3.86–3.89 (m, 1H, H-3), 3.99–4.05 (m, 2H, OCH_2CH_3), 4.41, (dd, J = 12.2 Hz, 1H, OCH_2Ph), 4.43 (dd, J = 12.2 Hz, 1H, OCH_2Ph), 6.75–7.30 (m, 9H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2 (CH_2CH_3), 29.8 (CH_2COO), 38.5 (C-4), 51.7 (C-5), 55.2 (OCH_3), 58.2 (NCH_2Ar), 60.3 (CH_2CH_3), 66.9 (C-2), 70.8 (CH_2Ph), 83.6 (C-3) ppm. MS (ESI, *m*/*z*): 384 ($M+H^+$, 100). HRESIMS calcd for $[C_{23}H_{29}NO_4+H]^+$: 384.2169. Found 384.2173.

4.10. Benzyl (2*R*,3*S*)-(2-ethoxycarbonylmethyl-3-hydroxypyrrolidin-1-yl)carboxylate 3

A solution of **13** (90 mg, 0.235 mmol) in ethanol (1.9 mL) was added dropwise to a stirred suspension of 10% Pd/C (72 mg) in ethanol (1.9 mL) containing formic acid (0.22 mL) at rt under N_2 atmosphere. After completion of the reaction, the mixture was diluted with ethanol (5 mL), filtered through a Celite pad, and washed repeatedly with ethanol. The filtrates were concentrated under reduced pressure. The residue was re-subjected to hydrogenolysis conditions to afford the 3-pyrrolidinol derivative, which without further purification, was used in the following reaction.

To an ice-bath cooled stirred solution of the crude (2*R*,3*S*)-3-pyrrolidinol derivative in CH_2Cl_2 were added successively triethylamine (0.06 mL) and benzyl chloroformate (0.05 mL). After being stirred at room temperature for 4 h, the reaction was quenched by water (2 mL). The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (eluent: EtOAc–PE = 0.8:1) to give **3**[19] as a pale yellow oil (43 mg, yield: 60%). $[\alpha]_D^{20} = -33.9$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3435, 3032, 2980, 2963, 2898, 1732, 1701, 1586, 1498, 1417 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, rotamers): δ 1.26 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.85–1.94 (m, 1H, H-4), 2.02–2.10 (m, 1H, H-4), 2.20–2.28 (m, 1H, CH_2COO), 2.85 (m, 0.87H, CH_2COO), 3.00 (s, 0.53H, O*H*), 3.12 (dd, J = 3.3, 16.4 Hz, 0.53H, CH_2COO), 3.40–3.51 (m, 1H, H-5), 3.62–3.78 (m, 1H, H-5), 4.00–4.20 (m, 2H, OCH_2CH_3), 4.26 (br s, 1H, H-2), 5.10–5.18 (m, 2H, $PhCH_2$), 7.24–7.40 (m, 5H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (CH_2CH_3), 30.9 (CH_2COO), 36.8 (C-4), 44.3 (C-5), 60.8 (C-2), 62.3 (CH_2CH_3), 66.8 (CH_2Ph), 75.2 (C-3), 127.8, 128.4, 127.9, 136.7 (Ph), 154.8 ($OCOCH_2Ph$), 171.5 (O*C*OEt) ppm. MS (ESI, *m*/*z*): 308 ($M+H^+$, 100), 330 ($M+Na^+$, 60).

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