Efficient Total Synthesis of (-)-Stemoamide

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ELECTRONIC SUPPLEMENTARY INFORMATION (ESI)

1) General Experimental Procedures

2) Experimental Procedures

\((S,S)-(\{\text{[tert-Butyl(dimethyl)silyl]oxy\}}\text{methyl})-1-[4-(\text{tetrahydro}-2H-\text{pyran}-2-\text{yloxy})\text{butyl}]\text{pyrrolidin-2-}\text{one}\) (6) S-3

\((S,S)-(\text{Hydroxymethyl})-1-[4-(\text{tetrahydro}-2H-\text{pyran}-2-\text{yloxy})\text{butyl}]\text{pyrrolidin-2-}\text{one}\) (7) S-3

\((2S)-5-\text{Oxo}-1-[4-(\text{tetrahydro}-2H-\text{pyran}-2-\text{yloxy})\text{butyl}]\text{pyrrolidin-2-}\text{carbaldehyde}\) (8) S-3

Methyl \((2E)-3-\{(2S)-5-\text{oxo}-1-[4-(\text{tetrahydro}-2H-\text{pyran}-2-\text{yloxy})\text{butyl}]\text{pyrrolidin-2-yl}\}\text{acrylate}\) (9) S-3

Methyl \((2E)-3-\{(2S)-1-[4-(\text{hydroxy} \text{butyl})-5-\text{oxopyrrolidin-2-yl}\}\text{acrylate}\) (10) S-4

Methyl \((2E)-3-\{(2S)-5-\text{oxo}-1-[4-\text{oxobutyl}]\text{pyrrolidin-2-yl}\}\text{acrylate}\) (11) S-4

SmI\(_2\)-promoted cyclization of \(11\) to \(12\) and \(13\) in the absence of HMPA S-5

\((3aR,10aS,10bS)-\text{Octahydro}-2H-\text{furo}[3,2-c]\text{pyrrolo[1,2-}\text{a}]\text{azepine-2,8(1H)-dione}\) (12) S-5

\((3aS,10aS,10bS)-\text{Octahydro}-2H-\text{furo}[3,2-c]\text{pyrrolo[1,2-}\text{a}]\text{azepine-2,8(1H)-dione}\) (13) S-5

\((3aR,10aS)-3a,4,5,6,10,10a-\text{Hexahydro}-2H-\text{furo}[3,2-c]\text{pyrrolo[1,2-}\text{a}]\text{azepine-2,8(9H)-dione}\) (15) S-5

SmI\(_2\)-promoted cyclization of \(11\) to \(16\) in the presence of HMPA S-6

\((3aS,10aS)-3a,4,5,6,10,10a-\text{Hexahydro}-2H-\text{furo}[3,2-c]\text{pyrrolo[1,2-}\text{a}]\text{azepine-...
2,8(9H)-dione (16)  S-6
SmI₂-promoted cyclization of 11 to 16 in the presence of HMPA  S-6
SmI₂-promoted cyclization of 18 to 12 and 13 in the absence of HMPA  S-6
SmI₂-promoted cyclization of 18 to 16 in the presence of HMPA  S-7
(1S,3aR,10aS,10bR)-1-Methyloctahydro-2H-furo[3,2-c]pyrrolo[1,2-a]azepine-2,8(1H)-dione; (-)-Stemoamide (1)  S-7

3) NMR spectra

1H NMR Spectrum of 6  S-8
13C NMR Spectrum of 6  S-9
1H NMR Spectrum of 7  S-10
13C NMR Spectrum of 7  S-11
1H NMR Spectrum of 9  S-12
13C NMR Spectrum of 9  S-13
1H NMR Spectrum of 10  S-14
13C NMR Spectrum of 10  S-15
1H NMR Spectrum of 11  S-16
13C NMR Spectrum of 11  S-17
1H NMR Spectrum of 15  S-18
13C NMR Spectrum of 15  S-19
1H NMR Spectrum of 16  S-20
13C NMR Spectrum of 16  S-21
1H NMR Spectrum of 1  S-22

General Experimental Procedures. Melting points were measured with a melting point apparatus and are uncorrected. IR spectra were recorded as thin films on sodium chloride plates. Otherwise noted, 1H and 13C NMR spectra were obtained for solutions in CDCl₃, and chemical shifts are reported on the δ scale using TMS as an internal standard of δ 0.00 for 1H-NMR spectra, and CDCl₃ as an internal standard or δ 77.00 for 13C NMR spectra, respectively (1H-NMR: 400 MHz, 13C NMR: 100 MHz). Reagents were purchased from commercial sources.
(5S)-(tBu-(dimethyl)silyl)oxy)methyl)-1-[4-(tetrahydro-2H-pyran-2-yloxy)butyl]pyrrolidin-2-one (6). To a stirred solution of the amide (5) (2.00 g, 8.73 mmol), 2-(4-bromobutoxy)tetrahydro-2H-pyran (4.10 g, 17.37 mmol), and tetrabutylammonium iodide (323 mg, 0.84 mmol) in DMF (88 mL) was added dropwise NaHMDS (1.9M in THF solution, 6.9 mL, 13.1 mmol) at -15 °C. The resulting mixture was stirred at the same temperature for 10 min, and at ambient temperature for 3 h. The mixture was treated with saturated aqueous NH₄Cl solution, diluted with H₂O, and extracted three times with CHCl₃. The combined organic extracts were washed twice with H₂O and brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. Elution with hexane-EtOAc (3:7, v/v) gave 6 (2.96 g, 88%) as a colorless oil. [α]°D +5.76 (c 1.0 CHCl₃); IR νmax: 3473, 2938, 2857, 1687, 1460 cm⁻¹; ¹H NMR δ: 4.50 (t, J = 4.2 Hz, 1H), 3.85-3.76 (m, 1H), 3.75-3.50 (m, 5H), 3.48-3.40 (m, 1H), 3.38-3.32 (m, 1H), 3.10-2.92 (m, 1H), 2.44-2.34 (m, 1H), 2.28-2.20 (m, 1H), 2.08-1.96 (m, 1H), 1.84-1.73 (m, 2H), 1.58-1.42 (m, 9H), 0.90 (s, 9H), 0.05 (s, 6H); ¹³C NMR δ: 175.2, 98.8, 67.0, 63.8, 62.3, 58.8, 40.5, 30.6, 30.5, 27.0, 25.6, 25.3, 24.2, 21.4, 19.5, 18.0, -5.7; HRMS Calcd for C₂₀H₄₀NO₄Si [M+H]+ 386.2726. Found 386.2721.

(5S)-(Hydroxymethyl)-1-[4-(tetrahydro-2H-pyran-2-yloxy)butyl]pyrrolidin-2-one (7). To a stirred solution of 6 (2.00 g, 5.19 mmol) in MeOH (26 mL) was added NH₄F (962 mg, 25.98 mmol) at room temperature and the resulting mixture was heated at reflux for 10 h. After concentration of the mixture in vacuo, a residue was taken up into 5% methanol in CHCl₃ and the whole solution was filtrated to remove the insoluble materials. The filtrate was concentrated to leave a residue, which was purification by column chromatography on silica gel. Elution with MeOH-EtOAc (5:95, v/v) furnished 7 as a colorless oil (1.34 g, 95%). [α]°D +6.4 (c 1.0); IR νmax: 3409, 2938, 1660, 1464 cm⁻¹; ¹H NMR δ: 4.50 (t, J = 4.2 Hz, 1H), 3.85-3.76 (m, 1H), 3.75-3.50 (m, 1H), 3.48-3.40 (m, 1H), 3.11-3.02 (m, 1H), 2.51-2.40 (m, 1H), 2.34-2.25 (m, 1H), 2.14-2.04 (m, 1H), 2.00-1.90 (m, 1H), 1.80-1.74 (m, 1H), 1.74-1.46 (m, 9H); ¹³C NMR δ: 175.8, 99.0, 67.0, 62.8, 62.6, 59.1, 40.5, 30.7, 30.5, 27.0, 25.4, 24.3, 21.2, 19.8; HRMS Calcd for C₁₄H₂₆NO₄ [M+H]+ 272.1862. Found 272.1846.

Methyl (2E)-3-[(2S)-5-oxo-1-[4-(tetrahydro-2H-pyran-2-yloxy)butyl]pyrrolidin-2-yl]acrylate (9). To a stirred solution of oxalyl chloride (1.52 mL, 17.96 mmol) in CH₂Cl₂ (22 mL) was added a solution of DMSO (1.9 mL, 26.75 mmol) in CH₂Cl₂ (4.5 mL) at -78 °C under argon, and the resulting solution was stirred at the same
temperature for 10 min. A solution of 7 (2.40 g, 8.86 mmol) in CH$_2$Cl$_2$ (15 mL) was added to the solution, and the whole was stirred at the same temperature for further 1 h. The mixture was treated with triethylamine (8.7 mL, 62.13 mmol), and warmed to room temperature over the period of 20 min. The solution was treated with H$_2$O and extracted with CHCl$_3$. The organic layer was washed with brine and dried over Na$_2$SO$_4$. Removal of the solvent under reduced pressure afforded the aldehyde 8, which without further purification, was used directly in the next step.

To a stirred solution of the crude aldehyde (8) (2.36 g, 8.77 mmol) in acetonitrile (43 mL) was added methyl (triphenylphosphoranylidene)acetate (3.82 g, 11.44 mmol), and the resulting mixture was stirred at room temperature for 12 h. Removal of the solvent under reduced pressure gave a residue, which was purified by column chromatography on silica gel. Elution with hexane-EtOAc (1:9, v/v) gave 9 (2.36 g, 82%) as a colorless oil. $\text{[α]}^{20}_D +5.3$ (c 0.9); IR $\nu_{\text{max}}$: 2947, 1725, 1687, 1437 cm$^{-1}$; $^1$H NMR $\delta$: 6.75 (dd, $J = 8.1, 15.6$ Hz, 1H), 5.95 (d, $J = 15.6$ Hz, 1H), 4.50 (t, $J = 4.2$ Hz, 1H), 4.27-4.20 (m, 1H), 3.87-3.80 (m, 1H), 3.77-3.70 (m, 4H), 3.68-3.60 (m, 1H), 3.52-3.46 (m, 1H), 3.41-3.35 (m, 1H), 2.90-2.82 (m, 1H), 2.50-2.20 (m, 3H), 1.86-1.75 (m, 2H), 1.74-1.46 (m, 9H); $^{13}$C NMR $\delta$: 174.6, 166.0, 146.6, 122.7, 98.9, 66.9, 62.4, 58.7, 51.8, 40.8, 30.7, 29.6, 27.0, 25.4, 24.9, 24.2, 19.7; HRMS Calcd for C$_{17}$H$_{28}$NO$_5$ [M+H]$^+$ 326.1967. Found 326.1945.

**Methyl (2$E$)-3-[(2$S$)-1-[4-(hydroxybutyl)-5-oxopyrrolidin-2-yl]acrylate (10).** To a stirred solution of 9 (2.84 g, 8.74 mmol) in MeOH (87 mL) was added p-TSA (166 mg, 0.87 mmol) at room temperature, and the resulting mixture was stirred at the same temperature for further 12 h. The reaction was quenched by addition of saturated aqueous NaHCO$_3$ solution and the aqueous layer was extracted with CHCl$_3$. The extract was washed with brine and dried over Na$_2$SO$_4$. Removal of the solvent under reduced pressure afforded the alcohol (10) (1.94 g, 92%) as a colorless oil. $\text{[α]}^{20}_D +7.5$ (c 1.0); IR $\nu_{\text{max}}$: 3401, 2946, 1720, 1666, 1436 cm$^{-1}$; $^1$H NMR $\delta$: 6.75 (dd, $J = 8.3, 15.7$ Hz, 1H), 5.95 (d, $J = 15.7$ Hz, 1H), 4.25 (dt, $J = 4.8, 8.0$ Hz, 1H), 3.75 (s, 3H), 3.65-3.55 (m, 3H), 2.94-2.83 (m, 1H), 2.50-2.25 (m, 4H), 1.86-1.77 (m, 1H), 1.60–1.45 (m, 4H); $^{13}$C NMR $\delta$: 175.0, 165.9, 146.4, 122.8, 62.1, 58.9, 51.8, 40.7, 29.6, 29.4, 24.8, 23.8; HRMS Calcd for C$_{12}$H$_{20}$NO$_4$ [M+H]$^+$ 242.1392. Found 242.1369.

**Methyl (2$E$)-3-{(2$S$)-5-oxo-1-[4-oxobutyl]pyrrolidin-2-yl}acrylate (11).** To a solution of oxalyl chloride (0.15 mL, 1.77 mmol) in CH$_2$Cl$_2$ (2 mL) was added a solution of DMSO (0.18 mL, 2.49 mmol) in CH$_2$Cl$_2$ (0.4 mL) at -78 °C under argon, and the
resulting solution was stirred at the same temperature for 10 min. A solution of alcohol 10 (200 mg, 0.83 mmol) in CH$_2$Cl$_2$ (2 mL) was added to the solution, and the whole was stirred at the same temperature for 1 h. After the mixture was treated with triethylamine (0.82 mL, 5.88 mmol), the whole was warmed up to room temperature over the period of 20 min. The solution was treated with H$_2$O, and extracted with CHCl$_3$. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to leave a residue, which was subjected to column chromatography on silica gel. Elution with MeOH-CHCl$_3$ (2:98, v/v) afforded the aldehyde (11) (168 mg, 85%) as a colorless oil. [$\alpha$]$^D_{20}$ +9.5 (c 1.0); IR $\nu_{\text{max}}$: 2915, 1720, 1670, 1435 cm$^{-1}$; $^1$H NMR $\delta$: 9.75 (s, 1H), 6.75 (dd, $J$ = 8.4, 15.5 Hz, 1H), 5.95 (d, $J$ = 15.5 Hz, 1H), 4.25 (dt, $J$ = 4.7, 8.1 Hz, 1H), 3.75 (s, 3H), 3.60-3.50 (m, 1H), 2.92-2.84 (m, 1H), 2.52-2.20 (m, 5H), 1.85-1.74 (m, 3H); $^{13}$C NMR $\delta$: 201.1, 175.0, 165.9, 146.1, 123.1, 58.8, 51.8, 41.1, 40.2, 29.4, 24.8, 19.7; HRMS Calcd for C$_{12}$H$_{17}$NO$_4$ [M]$^+$ 239.1157. Found 239.1185.

SmI$_2$-promoted cyclization of 11 to 12 and 13 in the absence of HMPA. To a stirred solution of the aldehyde (11) (100 mg, 0.42 mmol) in THF (21 mL) in the presence of MeOH (85 $\mu$L, 2.1 mmol) was added SmI$_2$ (0.2 M in THF solution, 10.5 mL, 2.1 mmol) at 0 °C under argon. After being stirred for 3 h, the resulting mixture was treated saturated aqueous NH$_4$Cl solution and extracted with CHCl$_3$. The organic layer was washed with brine and dried over Na$_2$SO$_4$. Evaporation of the solvent gave a mixture of 12 and 13 in 60% yield, in a ratio of ca. 0.9 : 1, based on the analysis of its $^1$H NMR spectrum. Spectroscopic data of 12$^{1}$ and 13$^{2,3}$ were similar to those reported in the literature.

(3a$^S$,10a$^S$)-3a,4,5,6,10,10a-Hexahydro-2H-furo[3,2-c]pyrrolo[1,2-a]azepine-2,8(9H)-dione (15). To a stirred solution of 12 (293 mg, 1.40 mmol) in THF (37 mL) was added LiHMDS (1.6M in THF solution, 3.5 mL, 5.60 mmol) at -78 °C. After being stirred at the same temperature for 30 min, phenylselenylenyl bromide (828 mg, 3.51 mmol) was added, and the resulting mixture was stirred for 1 h. After the reaction mixture was quenched by addition of 1 M hydrochloric acid, the aqueous phase was extracted with CHCl$_3$. The extract was washed with brine and dried over Na$_2$SO$_4$, and concentrated under reduced pressure to leave the selenide (14), which was then dissolved in CH$_2$Cl$_2$ (18 mL). The solution was cooled to 0 °C and treated with 30% hydrogen peroxide (27 mL). After the mixture was vigorously stirred for 1 h at the same temperature, the aqueous layer was extracted with CHCl$_3$. The organic layer was washed with brine and dried over Na$_2$SO$_4$, and concentrated under reduced pressure to leave a residue, which
was subjected to column chromatography on silica gel. Elution with MeOH-CHCl₃ (2:98, v/v) afforded 15 (347mg, 85 %) as a white solid: Mp 156-157 °C (lit.⁴ mp 157-158 °C); [α]D -204 (c = 0.4, CHCl₃) {lit.⁴ [α]D -224 (c = 0.4, CHCl₃)}. The spectroscopic data of 15 were comparable to those reported in the literature.⁴

(3aR,10aS,10bR)-Octahydro-2H-furo[3,2-c]pyrrolo[1,2-a]azepine-2,8(1H)-dione (16).
To a stirred solution of 15 (26.8 mg, 0.13 mmol) in MeOH (2.5 mL) was added NiCl₂ · 6H₂O (7.7 mg, 32.3 μmol) followed by NaBH₄ (20 mg, 0.53 mmol) at -30 °C. After being stirred for 3 h at the same temperature, the solution was treated with 1M HCl. The aqueous layer was extracted with CHCl₃, and the organic layer was washed with brine and dried over Na₂SO₄, and concentrated under reduced pressure to leave a residue, which was purified by column chromatography on silica gel. Elution with MeOH-CHCl₃ (2:98, v/v) afforded 16 (24.6 mg, 91%) as a colorless oil. [α]D²⁰ -97.8 (c 0.3) {lit.⁴ [α]D²⁰ -94.0 (c 0.4 CHCl₃)}. The spectroscopic data of 16 were comparable to those reported in the literature.

Sml₂-promoted cyclization of 11 to 16 in the presence of HMPA. To a stirred solution of the aldehyde (11) (80.9 mg, 0.34 mmol) in THF (17 mL) in the presence of MeOH (68.6 μL, 1.70 mmol) and HMPA (1.17 mL, 6.72 mmol) was added Sml₂ (0.2 M in THF solution, 8.5 mL, 1.69 mmol) at 0 °C under argon. After being stirred for 3 h, the resulting mixture was treated saturated aqueous NH₄Cl solution and extracted with CHCl₃. The organic layer was washed with brine and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with MeOH-CHCl₃ (2:98, v/v) gave 16 (39.2 mg, 55%) as a colorless oil, together with a small amount of its diastereoisomer (17). The spectroscopic data of 16 were identical with those of the authentic specimen obtained above. Although isolation of a minor product (17) was attempted, we could not obtain it in pure form, unfortunately, due to its small amount available.

Sml₂-promoted cyclization of 18 to 12 and 13 in the absence of HMPA. To a stirred solution of the aldehyde (11) (50 mg, 0.20 mmol) in THF (10.5 mL) in the presence of EtOH (58 μL, 0.99 mmol) was added Sml₂ (0.2 M in THF solution, 5.2 mL, 0.99 mmol) at 0 °C under argon. After being stirred for 3 h, the resulting mixture was treated saturated aqueous NH₄Cl solution and extracted with CHCl₃. The organic layer was
washed with brine and dried over Na₂SO₄. Evaporation of the solvent gave a mixture of 12 and 13 in 53% yield, in a ratio of ca. 0.7 : 1, based on the analysis of its ¹H NMR spectrum. Spectroscopic data of 12¹ and 13²,³ were similar to those reported in the literature.

**SmI₂-promoted cyclization of 18 to 16 in the presence of HMPA.** To a stirred solution of the aldehyde (18) (32 mg, 0.13 mmol) in THF (6.4 mL) in the presence of EtOH (38 μL, 0.65 mmol) and HMPA (0.44 mL, 2.53 mmol) was added SmI₂ (0.2 M in THF solution, 3.2 mL, 0.64 mmol) at 0 °C under argon. After being stirred for 3 h, the resulting mixture was treated saturated aqueous NH₄Cl solution and extracted with CHCl₃. The organic layer was washed with brine and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with MeOH-CHCl₃ (2:98, v/v) gave 16 and 17 in 49% yield in a ratio of 3.5 : 1.

**(1S,3aR,10aS,10bR)-1-Methyloctahydro-2H-furo[3,2-c]pyrrolo[1,2-a]azepine-2,8(1 H)-dione; (-)-Stemoamide (1).** To a stirred solution of the lactone (16) (37 mg, 0.18 mmol) in THF (2.3 mL) was added LiHMDS (1.6M in THF solution, 0.2 mL, 0.19 mmol) at -78 °C. After being stirred for 30 min, MeI (55 μL, 0.88 mmol) was added and the resulting mixture was stirred for 3 h at the same temperature. The mixture was allowed to warm to room temperature gradually and was stirred at room temperature for 20 h. After treatment with saturated aqueous NH₄Cl solution, the whole was extracted with EtOAc. The extract was washed with brine and dried over Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with MeOH-CHCl₃ (3:97, v/v) gave (-)-stemoamide (1) (32.2 mg, 82%) as a white solid: Mp 184-185 °C (lit.⁴ mp 185-186 °C); [α]⁰ D  -138 (c 0.2, MeOH) {lit.⁴ [α]⁰ D -141 (c 0.3 MeOH)}. The spectroscopic data of 1 were comparable to those reported in the literature.⁴

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**Current Data Parameters**

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- **PROCNO:** 1

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**Channel f1**
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- **DS:** 2
- **NS:** 16

**Current Data Parameters**

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**Current Data Parameters**

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MeO₂C-\(\text{(CH}_₂\text{)}₄\text{O\text{THP}}\)