TOTAL SYNTHESIS OF (-)-STEMOAMIDE USING RUTHENIUM-CATALYZED ENYNE METATHESIS REACTION

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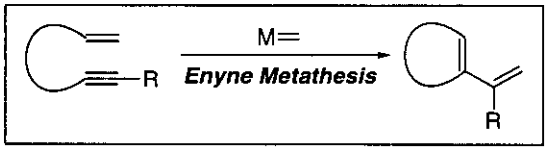
Abstract — A total synthesis of (-)-stemoamide was achieved from (-)-pyroglutamic acid using a ruthenium-catalyzed enyne metathesis as a key step, in 14 steps in 9% overall yield.

Stemoamide, which was first isolated from the roots and rhizomes of *Stemonaceous* plants, is a polycyclic alkaloid similar to stemonine, stenine and stemospironine, and possesses powerful insecticidal activity.[1,2] The first total synthesis of stemoamide was achieved by Williams.[3]

Intramolecular enyne metathesis[4] is a very attractive and unique tool for synthetic organic chemistry. We previously reported the enyne metathesis[5] using a ruthenium catalyst developed by Grubbs.[6]

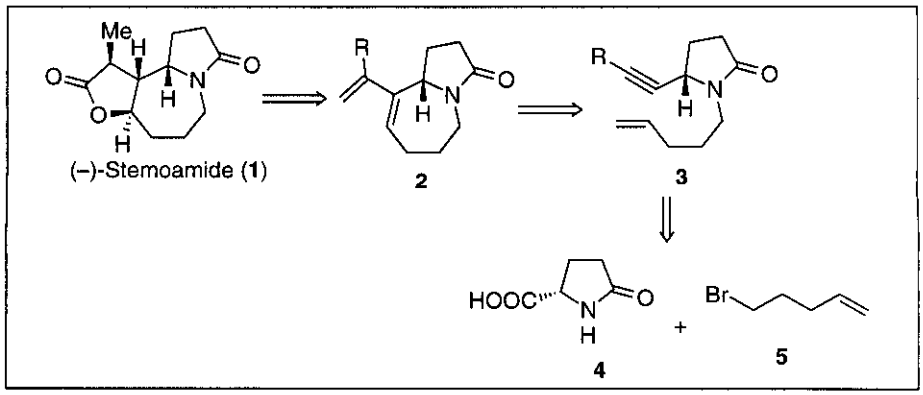


Scheme 1

The important characteristic features of intramolecular enyne metathesis are that the carbon-carbon bond formation between the alkene and alkyne occurs to give a cyclization product, and the alkylidene part of the alkene moiety migrates to the alkyne carbon (Scheme 1). The resultant diene moiety can be used for subsequent synthetic transformations.

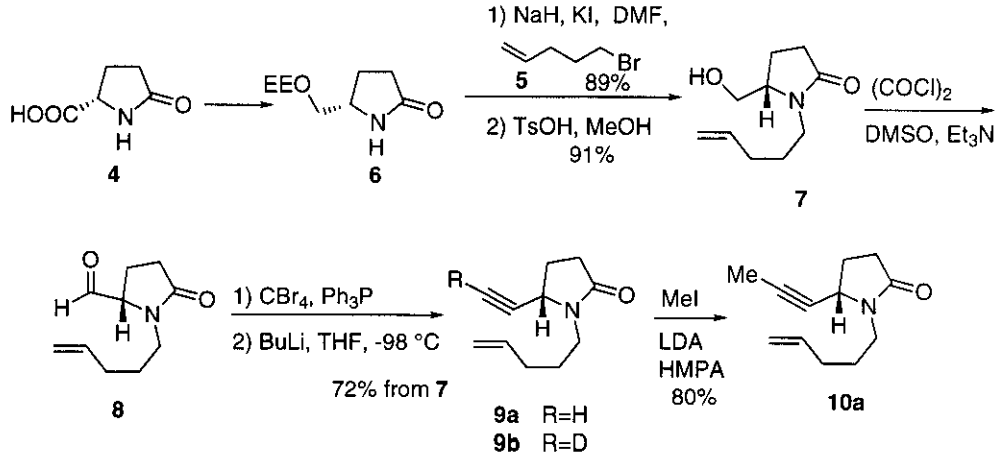
Dedicated to the memory of emeritus professor Dr. Shun-ichi Yamada (Tokyo University)

We now succeeded in a total synthesis of (-)-stemoamide from (-)-pyroglutamic acid using a ruthenium-catalyzed enyne metathesis[7] developed by Grubbs[6d] and our group,[5] in 14 steps. Our retrosynthetic analysis of (-)-stemoamide is shown in Scheme 2. If the enyne metathesis of compound (**3**) is realized using a ruthenium catalyst, cyclized product (**2**) should be formed. Using the diene part of **2**, stemoamide (**1**) should be synthesized. The enyne (**3**) should be prepared from (-)-pyroglutamic acid (**4**) and 5-bromo-1-pentene (**5**).



Scheme 2 Retrosynthetic Analysis

The starting enyne was prepared from (-)-pyroglutamic acid, which was converted into compound (**6**) as described in the literature (Scheme 3).[8]

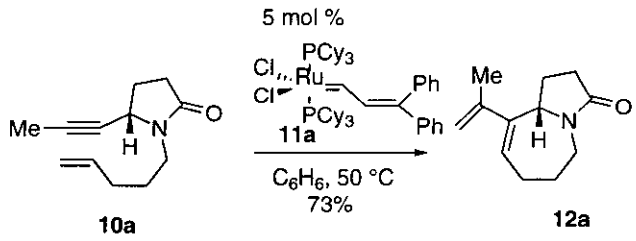


Scheme 3 Synthesis of Enynes

Alkylation of the sodium salt of **6** with 5-bromo-1-pentene (**5**) proceeded smoothly in DMF, and produced compound was deprotected with TsOH in MeOH to give alcohol (**7**) in high yield. Oxidation of **7** with oxalyl chloride and DMSO gave aldehyde (**8**). However,

when the crude aldehyde was purified by column chromatography on silica gel, the proton of the aldehyde on NMR spectrum became smaller. Thus, dibromoolefination was carried out without isolation of **8**. To the CH_2Cl_2 solution of oxalyl chloride (2 equiv.) and DMSO (4 equiv.) was added **7** (1 equiv.) at -78 °C, and then NEt_3 (10 equiv.) was added at -50 °C, and the entire solution was stirred at 0 °C for 30 min. To this solution were added CBr_4 (4 equiv.) and PPh_3 (8 equiv.) at 0 °C, and the solution was stirred at room temperature for 3 h. After the usual work up, the desired dibromoalkene was obtained in 87% yield from **7**. The resultant dibromoalkene was treated with BuLi at -98 °C to give enyne (**9a**). When compound (**9a**) was treated with 1.1 equiv. of LDA in the presence of 1.2 equiv. of HMPA and then 10 equiv. of D_2O was added, deuterated product (**9b**) was obtained in 83% yield. It means that the methylation would occur at the terminal alkyne, not at the carbon α to amide carbonyl, under these reaction conditions. Thus enyne (**9a**) was treated with an equimolar amount of LDA and then an excess amount of MeI to give enyne (**10a**) in 80% yield.

When a benzene solution of enyne (**10a**) and a catalytic amount of ruthenium catalyst (**11a**) (5 mol%) was stirred at 50 °C for 11 h, enyne metathesis proceeded smoothly to give a five-seven fused compound (**12a**) in 73% yield (Scheme 4).



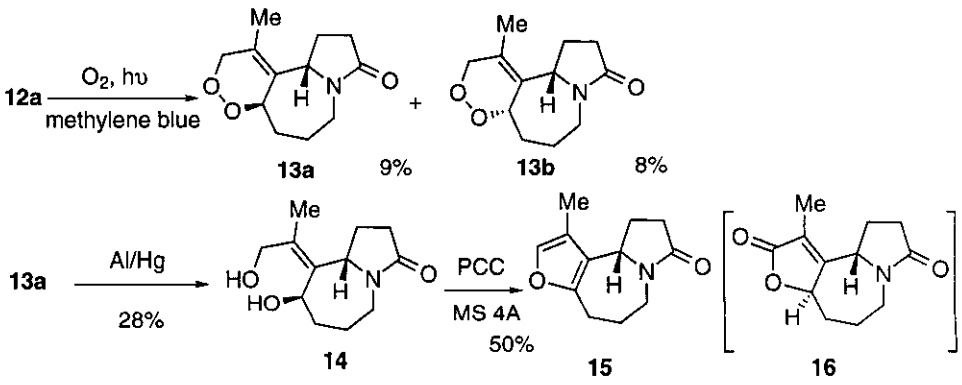
10a 12a

Scheme 4 Cyclization of Enyne (**10a**) Using Ruthenium Catalyst (**11a**)

Photo-irradiation of **12a** in the presence of methylene blue under oxygen gave two products (**13a** and **13b**) in yields of 9% and 8%, respectively, along with the starting material (51%) (Scheme 5). Compound (**12a**) was treated with Al/Hg to give diol (**14**) in yield of 28% which was treated with PCC, but the desired lactone (**16**) was not formed and furan derivative (**15**) was obtained in 50% yield. Various attempts were made to convert **14** into **16**, but the good results were not obtained.[9]

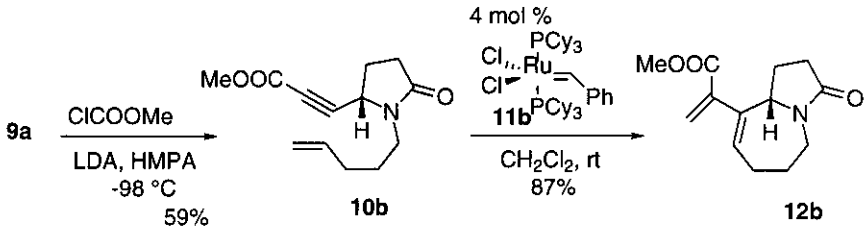
The cause of the low yield of the desired products (**13a** and **13b**) is believed to be the fact that the two double bonds of **12a** are not conjugated. The chemical shifts of the vinylic

protons of **12a** [4.90 (br s, 1 H), 4.95 (br s, 1 H), 5.92 (dd, J = 5.7, 9.1 Hz, 1 H)] appear at a higher field than those of the usual vinylic proton of the conjugated diene on the NMR spectrum. With regard to enyne metathesis, we previously reported the effects of the substituents on the alkyne.[5]



Scheme 5

Enyne metathesis with a carbomethoxy group on the alkyne gives a cyclized product in low yield, since the conjugated diene with a carbomethoxy group generated in this reaction is unstable under these reaction conditions. However, the diene of this cyclized product (**12b**) would not be conjugated because of the steric effect.

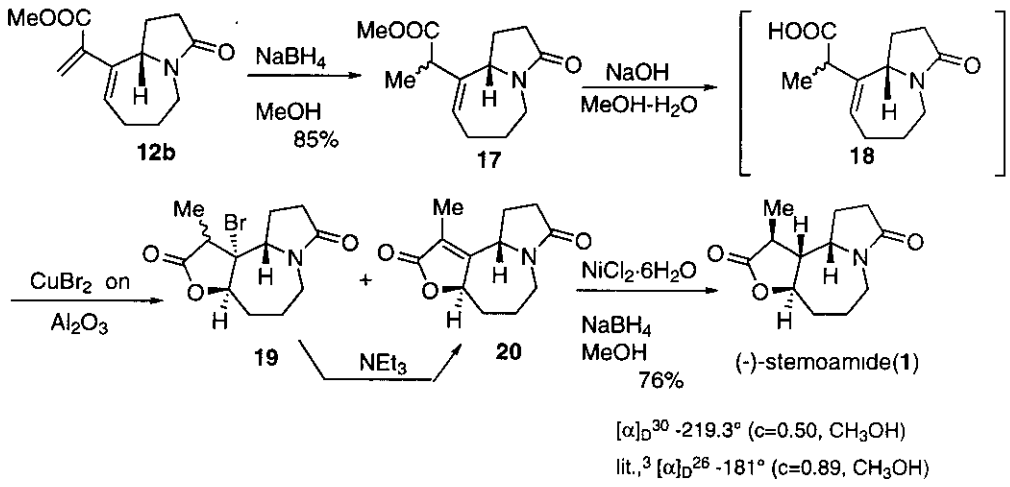


Scheme 6 Cyclization of Enyn es Using Ruthenium Catalyst (**11b**)

Thus, enyne (**10b**) having carbomethoxy group on the alkyne was synthesized from **9a**, and it was subjected to the enyne metathesis. We were very surprised to find that when a CH_2Cl_2 solution of enyne (**10b**) was stirred in the presence of a catalytic amount of ruthenium catalyst (**11b**)[6c] (4 mol %) at room temperature for 5 h, the desired metathesis product (**12b**) was obtained in 87% yield.

Treatment of **12b** with $NaBH_4$ gave **17** as two inseparable isomers, which were hydrolyzed

to give the corresponding carboxylic acid (**18**) (Scheme 7). Bromolactonization[10] of **18** proceeded smoothly *via* 5-*endo*-trig. cyclization and two products (**19** and **20**) were obtained in yields of 25% and 31%, respectively. Compound (**19**) could be easily converted into **20** by treatment with NEt_3. The stereochemistries of these compounds were not determined at this stage. However, based on a molecular modeling study, it was thought that the carboxylate would attack from the β-face of the olefin in bromolactonization because of the stability of the product, and the bromine was expected to be oriented *anti* to the oxygen.



Scheme 7 Synthesis of (–)-Stemoamide

Treatment of enone (**20**) with $NaBH_4$ in the presence of $NiCl_2 \cdot 6H_2O$ in MeOH[11] gave (-)-stemoamide (**1**), whose melting point, spectral data, and $[\alpha]_D$ value agreed with those reported.[2g,3] In this reaction, the hydride must be introduced to the β-face due to steric requirements, and the methyl group is placed *cis* to the ring-junction proton because of thermodynamic stability.

Thus, the total synthesis of (-)-stemoamide (**1**) was accomplished from (-)-pyroglutamic acid in 14 steps in 9% overall yield using ruthenium-catalyzed enyne metathesis as a key step.

ACKNOWLEDGMENT

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EXPERIMENTAL SECTION

All manipulations were performed under an argon atmosphere using standard Schlenk techniques, and the solution of the catalytic reaction was degassed through freeze-pump-thaw cycle. Solvents were distilled under an argon atmosphere from sodium benzophenone ketyl (THF) or CaH_2 (DMF and CH_2Cl_2). All other reagents and solvents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (70-230 mesh, 60 Å), and flash chromatography was performed on silica gel 60 (230-400 mesh, 60 Å) using the indicated solvent. Melting points are uncorrected.

(*S*)-5-Hydroxymethyl-1-(4-pentenyl)-2-pyrrolidinone (7). To a solution of NaH (15.6 mg, 0.65 mmol) and KI (119 mg, 0.717 mmol) in DMF (1.0 mL) was added a solution of **6** (111 mg, 0.591 mmol) in DMF (2 mL) at 0 °C, and the mixture was stirred at rt for 30 min. To the solution was added 5-bromo-1-pentene (84 mg, 0.709 mmol), and the resulting mixture was warmed at 50 °C for 3 h. Saturated NH_4Cl solution was added, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 3/1) to give a colorless oil of the alkylated product (135 mg, 89%). The solution of this compound (1.93 g, 7.54 mmol) and $TsOH•H_2O$ (29 mg, 0.152 mmol) in MeOH (60 mL) was stirred at rt for 3 h and concentrated. The residue was dissolved in ethyl acetate and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (AcOEt/MeOH, 10/1) to give a colorless oil of **7** (1.25 g, 91%). $[\alpha]_D^{28}$ +12.2° (*c* 1.07, MeOH); IR (neat) 3382, 1662 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.8, 10.2, 6.8 Hz, 1 H), 5.03 (br d, *J* = 16.8 Hz, 1 H), 4.98 (br d, *J* = 10.2 Hz, 1 H), 3.80 (dd, *J* = 11.5 Hz, 1 H), 3.72-3.59 (m, 3 H), 3.00 (ddd, *J* = 13.9, 9.0, 5.1 Hz, 1 H), 2.47 (ddd, *J* = 17.1, 9.9, 7.6 Hz, 1 H), 2.31 (ddd, *J* = 15.4, 10.2, 5.2 Hz, 1 H), 2.15-2.03 (m, 3 H), 1.97 (m, 1 H), 1.68 (m, 1 H), 1.59 (m, 1 H); ^{13}C-NMR (67.8 MHz,

$CDCl_3$) δ 175.9, 137.5, 115.0, 62.4, 59.0, 40.1, 31.0, 30.4, 26.4, 21.1; LRMS *m/z* 183, 152, 110, 98, 84, 41; HRMS calcd for $C_{10}H_{17}NO_2$ (M^+) 183.1187, found 183.1267.

(*S*)-5-Ethynyl-1-(4-pentenyl)-2-pyrrolidinone (9a). To a solution of oxalyl chloride (1.35 g, 14.1 mmol) in CH_2Cl_2 (15 mL) was added DMSO (2.0 mL, 9.28 mmol) in CH_2Cl_2 (6 mL) at -60 °C and the solution was stirred for 5 min. A solution of **7** (1.16 g, 6.35 mmol) in CH_2Cl_2 (10 mL) was added, and the mixture was stirred at the same temperature for 20 min. To this solution, Et_3N (8.9 mL, 63.9 mmol) was added, and the mixture was warmed to 0 °C. A solution of CBr_4 (8.42 g, 25.4 mmol) and PPh_3 (13.3 g, 50.7 mmol) in CH_2Cl_2 (31 mL) was added to the CH_2Cl_2 solution of the oxidated product at 0 °C, and the solution was stirred at the same temperature for 3 h. The reaction mixture was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 3/1, 2/1 and 1/1) to give a colorless oil of the dibromoalkene (1.85 g, 87%). To the solution of dibromoalkene (1.59 g, 4.72 mmol) in THF (32 mL) was added BuLi (1.64 M hexane solution, 9.5 mL, 15.6 mmol), and the solution was stirred at -98 °C for 15 min. To this solution was added propionic acid (2 M THF solution, 8.0 mL, 16.0 mmol), and the solution was warmed to rt. Water was added, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 2/1) to give a colorless oil of **9a** (605 mg, 72 %). $[\alpha]_D^{29}$ -11.74° (*c* 1.62, MeOH); IR (neat) 3226, 2113, 1688, 1640 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.3, 6.5 Hz, 1 H), 5.07-4.94 (m, 2 H), 4.32 (m, 1 H), 3.63 (ddd, *J* = 13.9, 8.7, 7.1 Hz, 1 H), 3.12 (ddd, *J* = 13.9, 8.3, 5.6 Hz, 1 H), 2.59-2.22 (m, 3 H), 2.40 (d, *J* = 2.2 Hz, 1 H), 2.15-2.02 (m, 3 H), 1.77-1.53 (m, 2 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) d 174.0, 137.5, 115.0, 81.4, 73.3, 61.3, 48.8, 40.5, 30.9, 29.9, 26.1; LRMS *m/z* 177, 152, 138, 136, 122, 108, 84, 69, 39.

(*S*)-1-(4-Pentenyl)-5-(1-propynyl)-2-pyrrolidinone (10a). To a solution of diisopropylamine (0.34 mL, 2.43 mmol) in THF (10 mL) was added BuLi (1.73 M hexane solution, 1.25 mL, 2.16 mmol) at -78 °C, and the solution was stirred at 0 °C for 10 min. A solution of **9a** (357 mg, 2.02 mmol) and HMPA (0.42 mL, 2.41 mmol) in THF (10 mL) was added, and the mixture was stirred at 0 °C for 1 h. To the solution was added MeI

(0.64 mL, 10.3 mmol) and the solution was warmed to rt. Saturated NH_4Cl solution was added, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 2/1) to give a colorless oil of **10a** (308 mg, 80 %). IR (neat) 3296, 2108, 1686, 1640 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.3, 6.53 Hz, 1 H), 5.08-4.94 (m, 2 H), 4.32-4.24 (m, 1 H), 3.61 (ddd, *J* = 13.7, 8.5 , 7.3 Hz, 1 H), 3.11 (ddd, *J* = 13.7 , 8.1, 5.7 Hz, 1 H), 2.55-2.20 (m, 2 H), 2.12-1.54 (m, 6 H), 1.83 (d, *J* = 2.2 Hz, 3 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 174.1, 137.7, 114.9, 81.2, 76.9, 49.3, 40.4, 31.1, 30.1, 26.7, 26.4, 3.4; LRMS *m/z* 191, 176, 150, 136, 122, 68, 41.

(*S*)-5-(Methoxycarbonylethynyl)-1-(4-pentenyl)-2-pyrrolidinone (10b). To a solution of diisopropylamine (0.32 mL, 2.28 mmol) in THF (10 mL) was added BuLi (1.64 M hexane solution, 1.25 mL, 2.05 mmol) at -78 °C, and the solution was stirred at 0 °C for 10 min. A solution of **9a** (341 mg, 1.92 mmol) and HMPA (0.37 mL, 2.13 mmol) in THF (7.8 mL) was added, and the mixture was stirred at 0 °C for 1 h. To a solution of ClCOOMe (0.64 mL, 10.3 mmol) in THF (3 mL) was added the lithium acetylide solution at -98 °C, and the solution was stirred at the same temperature for 1 h and warmed to rt. Saturated NH_4Cl solution was added, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 3/2) to give a pale yellow oil of **10b** (306 mg, 68%). $[\alpha]_D^{29}$ -39.22° (*c* 1.04, MeOH); IR (neat) 2238, 1714, 1642, 1258, 1092 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.24 (ddd, *J* = 17.0, 10.3, 6.5 Hz, 1 H), 5.02 (br d, *J* = 17.0 Hz, 1 H), 4.98 (br d, *J* = 10.3 Hz, 1 H), 4.44(dd, *J* = 8.1, 4.4 Hz, 1 H), 3.79 (s, 3 H), 3.63 (ddd, *J* = 14.1, 8.7, 7.1 Hz, 1 H). 3.12 (ddd, *J* = 14.1, 8.3, 5.5 Hz, 1 H), 2.60-2.30 (m, 3 H), 2.25-2.00 (m, 3 H), 1.80-1.50 (m, 2 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 174.2, 153.6, 137.7, 115.5, 85.0, 76.7, 53.2, 49.2, 41.2, 31.3, 29.9, 26.7, 25.8; LRMS *m/z* 235, 220, 204, 176, 152, 59.

(*S*)-2-(1-Methylethenyl)-7-azabicyclo[5.3.0]dec-2-en-8-one (12a). A solution of **10a** (194 mg, 1.01 mmol) and ruthenium complex (**11a**) (36.7 mg, 40.8 mmol) in benzene (30 mL) was warmed at 50 °C for 11 h. The solution was quenched by opening to air and concentrated. The residue was purified by column chromatography on silica

gel (hexane/AcOEt, 1/1) to give a pale yellow oil of **12a** (143 mg, 73%). IR (neat) 1687, 1560 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.92 (dd, *J*= 5.5, 9.1 Hz, 1 H), 4.95 (br s, 1 H), 4.90 (br s, 1 H), 4.63-4.54 (m, 1 H), 4.07 (ddd, *J*= 13.7, 8.7, 3.0 Hz, 1 H), 2.91 (ddd, *J*= 13.7 , 8.7, 8.7 Hz, 1 H), 2.48-2.26 (m, 4 H), 2.15-1.96 (m, 2 H), 1.95-1.83 (m, 1 H), 1.89 (s, 3 H), 1.78-1.60 (m, 1 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 174.6, 142.0, 141.4, 126.4, 111.8, 62.4, 38.7, 30.4, 27.0, 24.6, 22.2, 21.9; LRMS *m/z* 191, 176, 162, 150, 41; HRMS calcd for $C_{12}H_{17}NO$ (M^+) 191.1103, found 191.1333.

(1*S*,7*R*)-3-Methyl-11-aza-5,6-dioxatricyclo[9.3.0.0^{2,6}]tetradec-2(3)-en-12-one (13a). (1*S*,7*S*)-3-Methyl-11-aza-5,6-dioxatricyclo[9.3.0.0^{2,6}]tetradec-2(3)-en-12-one (13b). A solution of **12a** (100 mg, 0.524 mmol) and methylene blue (10.2 mg, 31.9 μmol) in $CHCl_3$ (5.2 mL) was irradiated by tungsten lamp (150 W) under oxygen atmosphere at rt for 18 h. The solution was diluted with $CHCl_3$. To the solution was added activated carbon, the solution was filtered and concentrated. The redidue was purified by column chromatography on silica gel (hexane/AcOEt, 2:1 then 1:1 then AcOEt) to give colorless oil of **13a** (10.0 mg , 44.8 μmol) and **13b** (9.6 mg, 43.0 μmol). **13a**: IR (neat) 1674, 1422 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.70 (br s, 1 H), 4.51 (br s, *J*= 15.7 Hz, 1 H), 4.27 (br s, *J*= 15.7 Hz, 1 H), 4.25 (dd, *J*= 9.0, 5.3 Hz, 1 H), 3.76 (ddd, *J*= 5.4, 3.7 Hz, 1 H), 3.07 (ddd, *J*= 13.9, 10.6, 3.1 Hz, 1 H), 2.60 (ddd, *J*= 17.0, 10.4, 6.0 Hz, 1 H), 2.52-2.37 (m, 3 H), 2.23 (ddt, *J*= 13.6, 10.4, 5.3 Hz, 1 H), 1.99 (m, 1 H), 1.85 (m, 1 H), 1.78 (m, 1 H), 1.72 (s, 3 H); ^{13}C-NMR ($CDCl_3$) δ 173.5, 131.0, 128.8, 80.0, 73.7, 57.6, 42.6, 30.2, 29.2, 22.7, 22.0, 14.8. **13b**: IR (neat) 3054, 1682, 1416; ^{1}H-NMR ($CDCl_3$) δ 4.66 (br d, *J*= 16.1 Hz, 1 H), 4.58 (br t, *J*= 7.9 Hz, 1 H), 4.19 (br d, *J*= 10.4 Hz, 1 H), 4.09 (br d, *J*= 16.1 Hz, 1 H), 2.48 (ddd, *J*= 13.9, 13.7, 1.9 Hz, 1 H), 2.44-2.30 (m, 3 H), 2.20 (m, 1 H), 2.05 (ddt, *J*= 13.1, 10.4, 4.6 Hz, 1 H), 1.81-1.75 (m, 1 H), 1.70 (s, 3 H), 1.68-1.58 (m, 2 H).

3-Methyl-10-aza-5-oxotricyclo[8.3.0.0^{2,6}]trideca-3,2(6)-dien-11-one (15). A suspension of **14** (1.2 mg, 5.3 μmol), pyridinium chlorochromate (6.2 mg, 28.8 μmol) and molecular sieves 4A (26.6 mg) in CH_2Cl_2 (2.0 mL) was stirred at 0 °C for 25 min. The solution was diluted with Et_2O and filtered through a short column of Florisil. The filtrate was concentrated, and the residue was purified by preparative TLC (AcOEt/MeOH, 10/1) to give a colorless oil of **15** (0.6 mg, 55%). IR (neat) 1668, 1560, 1264, 1100 cm^{-1};

^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.04 (br s, 1 H), 4.62 (dd, *J*= 7.1, 7.0 Hz, 1 H), 4.24 (dt, *J*= 13.9, 5.0 Hz, 1 H), 2.89-2.79 (m, 2 H), 2.73 (dt, *J*= 16.4, 6.7 Hz, 1 H), 2.53-2.41 (m, 2 H), 2.02-1.87 (m, 2 H), 1.97 (s, 3 H), 1.68-1.47 (m, 2 H); LRMS *m/z* 205, 190, 176, 162, 148.

(*S*)-2-(1-Methoxycarbonylethenyl)-7-azabicyclo[5.3.0]dec-2-en-8-one (12b). A solution of **10b** (191 mg, 0.81 mmol) and ruthenium complex (**11b**) (29.2 mg, 35.5 mmol) in CH_2Cl_2 (27 mL) was stirred at room temperature for 5 h. The solution was quenched by opening to air and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 1/1) to give a pale yellow oil of **12b** (165 mg, 87%).$[\alpha]_D^{32}$ -32.9° (*c* 1.37, MeOH); IR (neat) 1720, 1688, 1616, 1216, 1160 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.11 (d, *J*= 1.4 Hz, 1 H), 5.83 (ddd, *J*= 8.1, 5.0, 0.7 Hz, 1 H), 5.65 (d, *J*= 1.4 Hz, 1 H), 4.57 (m, 1 H), 4.10 (ddd, *J*= 13.7, 6.9, 6.7 Hz, 1 H), 3.78 (s, 3 H), 3.06 (ddd, *J*= 13.7, 6.9, 6.5 Hz, 1 H), 2.40-1.75 (m, 8 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 174.6, 166.7, 142.1, 140.1, 131.4, 126.1, 60.9, 52.0, 40.3, 29.9, 25.7, 25.0, 24.3; LRMS *m/z* 235, 220, 204, 176, 150.

(1*S*,3*R*)-3-Hydroxy-2-(hydroxy-2-propylidene)-8-azabicyclo[5.3.0]decan-8-one (14). To a solution of **13a** (4.9 mg, 22.0 mmol) in THF/H_2O (20/1, 1.0 mL) was added Al/Hg until the spot of the starting material disappeared on TLC. The solution was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (AcOEt/MeOH, 10:1) to give a colorless oil of **14** (1.4 mg, 28%). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.20 (br d, *J*= 5.0 Hz, 1H), 4.57 (m, 1 H), 4.33 (d, *J*= 10.0 Hz, 1 H), 3.98 (d, *J*= 10.0 Hz, 1 H), 2.59-2.28 (m, 3 H), 2.20-1.88 (m, 3 H), 1.83 (s, 3 H), 1.69-1.54 (m, 2 H), 1.46 (dt, *J*= 10.5, 4.0 1 H), 1.25 (br s, 1 H); LRMS *m/z* 225, 207, 192, 178, 164, 150, 136.

(7*S*)-6-(1-Methoxycarbonylethyl)-7-azabicyclo[5.3.0]dec-2-en-8-one (17). To a solution of **12b** (10.2 mg, 0.432 mmol) in MeOH (9.0 mL) was added $NaBH_4$ (131 mg, 3.46 mmol) at 0 °C, and the solution was stirred at the same temperature for 2 h. Saturated NH_4Cl solution was added, and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 1/1) to give a pale yellow oil of **17** (87.6 mg, 85 %). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.91 (dd, *J*= 8.0, 2.8 Hz, 1 H), 3.95 (ddd, *J*= 13.9, 9.7, 5.4 Hz, 1 H), 3.82 (br d, *J*= 7.7 Hz, 1 H), 3.31 (q, *J*= 7.6 Hz, 1 H), 3.07 (dt,

J = 13.9, 5.5 Hz, 1 H), 2.89-2.80 (m, 1 H), 2.58-2.43 (m, 1 H), 2.19 (m, 3 H), 1.55-1.54 (m, 1 H), 1.43 (d, J = 7.6 Hz, 3 H).

(6*R*,1*S*)-3-Methyl-10-aza-5-oxatricyclo[8.3.0^{2,6}]tridec-2(3)-en-11-one (20). A solution of **17** (85.1 mg, 0.359 mmol) in MeOH(3.8 mL) and aq. 1N NaOH solution (3.8 mL) was stirred at 0 °C for 7 h. The solution was neutralized by 10% HCl and concentrated. The residue was acidified by conc. HCl, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in $CHCl_3$ (29 mL), and $CuBr_2$ on alumina (1.25 g) was added. The mixture was warmed at 65 °C for 60 h. After filtration, the solid was washed with MeOH, and the filtrate was concentrated. Water was added to the residue, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in ethyl acetate (7 mL), and Et_3N (0.1 mL, 0.718 mmol) was added and the solution was stirred at rt for 14 h. The reaction solution was washed with 10% HCl, brine, saturated $NaHCO_3$ solution, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (AcOEt) to give colorless crystals of **20** (39.4 mg, 50 %). mp 127-129 °C; $[\alpha]_D^{27}$ -246.3° (*c* 0.63, MeOH); IR (neat) 1748, 1682, 1266, 1092, 1016 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.87 (br d, J = 11.6 Hz, 1 H), 4.74 (dd, J = 7.9, 7.6 Hz, 1 H), 4.29 (br d, J = 14.3 Hz, 1 H), 2.56-2.45 (m, 5 H), 1.89 (s, 3 H), 1.88 (m, 1 H), 1.79-1.69 (m, 2 H), 1.34 (ddt, J = 13.4, 11.7, 3.5 Hz, 1 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 174.1, 173.2, 164.7, 123.8, 81.2, 57.6, 43.5, 34.8, 30.0, 25.7, 25.6, 8.9; LRMS *m/z* 221, 206, 177, 150, 136, 79, 55; HRMS calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1187, found 221.1037.

(-)-Stemoamide (1). To a solution of **20** (13.1 mg, 59.2 mmol) in MeOH (0.9 mL) was added $NiCl_2$•$6H_2O$ (3.5 mg, 14.7 mmol) and $NaBH_4$ (9.2 mg, 238 mmol) at -30 °C, and the mixture was stirred at the same temperature for 1.6 h. The resulting mixture was diluted with CH_2Cl_2. The organic layer was washed with 10% HCl, saturated $NaHCO_3$ solution, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative thin layer chromatography on silica gel (AcOEt/MeOH, 10/1) to give colorless crystals of stemoamide (**1**) (10.1 mg), which was recrystallized (6.3 mg, 48%) from AcOEt. mp 187-188 °C; $[\alpha]_D^{30}$ -219.3° (*c* 0.50, MeOH); IR (neat) 1754, 1658 cm^{-1}; ^{1}H-NMR (500 MHz,

$CDCl_3$) δ 4.20 (dt, *J* = 10.3, 3.1 Hz, 1 H), 4.16 (m, 1 H), 3.99 (dt, *J* = 10.8, 6.3 Hz, 1 H), 2.65 (dd, *J* = 14.1, 12.3 Hz, 1 H), 2.60 (dq, *J* = 12.5, 6.9 Hz, 1 H), 2.45-2.38 (m, 4 H), 2.05 (m, 1 H), 1.87 (m, 1 H), 1.72 (dt, *J* = 22.7, 10.7 Hz, 1 H), 1.58-1.50 (m, 2 H), 1.31 (d, *J* = 6.9 Hz, 3 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 177.3, 174.0, 77.6, 55.8, 52.7, 40.2, 37.3, 34.8, 30.5, 25.6, 22.5, 14.1; LRMS *m/z* 223, 208, 180, 138, 98.

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