JOC*Note*

Total Synthesis of (−)-Stemoamide

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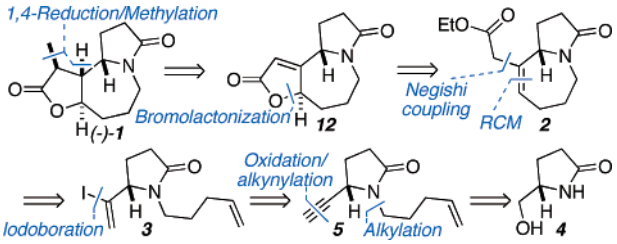

A stereocontrolled total synthesis of (−)-stemoamide (**1**) is presented. The synthesis starts from commercially available (*S*)-pyroglutaminol (**4**). A chemoselective iodoboration of **5** was used to access key intermediate **3**. The β,γ-unsaturated azepine derivative **2** was obtained via a Pd(0)-catalyzed sp^2-sp^3 Negishi cross-coupling using a Reformatsky nucleophile followed by a ring-closing metathesis reaction. The required C8−C9 *trans*-stereochemistry of **1** was accessed through a stereoselective bromolactonization/1,4-reduction sequence.

The *Stemona* class of natural products, comprising 42 isolated structures, represents a family of polycyclic alkaloids structurally characterized by the presence of a pyrrolo[1,2-*a*]azepine core, and several members also contain an α-methyl-γ-butyrolactone subunit (Figure 1).[1] This class of natural products has received considerable attention in recent years due to their interesting biological properties as well as their structural diversity, which makes them suitable targets for total synthesis.[2] Traditionally, the root extracts of *Stemona tuberosa* have been employed in Chinese and Japanese folk medicine for respiratory disorders and also as an antihelminthic.[1] Of the plethora of alkaloids present in *Stemona tuberosa*, (−)-stemoamide (**1**), isolated in 1992 by Xu and co-workers,[1a] is structurally the simplest member of the *Stemona* class containing a tricyclic core and four contiguous stereogenic centers. The first total synthesis of **1** was reported by Williams and co-workers in 1994.[2a]

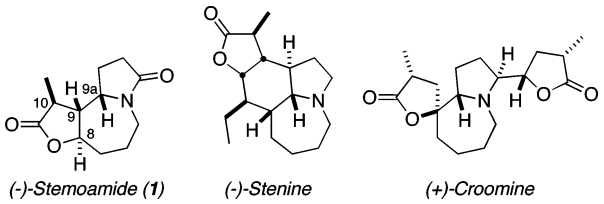

FIGURE 1. Some *Stemona* alkaloids.

Our initial retrosynthetic analysis of (−)-stemoamide **1** (Scheme 1) set out to install the γ-butyrolactone functionality with the correct C8−C9 *trans*-stereochemistry via a stereoselective hydroboration of β,γ-unsaturated azepine **2**. The late-stage α-methylation of the γ-butyrolactone is well precedented in the literature.[2e,f,3] The pyrrolo[1,2-*a*]azepine core was to be derived from vinyliodide **3** through a Negishi/ring-closing metathesis (RCM) sequence. In a previous study, the azepine moiety was constructed by a similar enyne metathesis reaction,[2b] which gave some credence to our analysis.

Our synthesis began with protection of the primary alcohol in **4** as the corresponding TBS-ether **6** (Scheme 2). N-Alkylation of the lactam using NaHMDS at low temperature was followed by removal of the TBS group to cleanly give alcohol **7** in excellent yield. Conversion of compound **7** into alkyne **5** was realized by a high yielding two-step procedure: Swern oxidation followed by treatment of the crude aldehyde with Ohira−Bestmann[4] diazophosphonate **8** and K_2CO_3 in MeOH. The vinyliodide moiety in **3** was installed by a chemoselective iodoboration of the alkyne functionality in the presence of a primary alkene using *B*-I-9-BBN at low temperature,[5] which led to **3** in good yield. The subsequent Pd(0)-catalyzed sp^2-sp^3 coupling to install the β,γ-unsaturated ester required some optimization. Subjecting a mixture of vinyliodide **3** and Pd-$(PPh_3)_4$ in THF/DMPU to Reformatsky reagent **9**, derived from ethyl α-bromoacetate,[6] gave compound **10** in high yield. The use of 15−25 vol % DMPU as cosolvent proved to be crucial for the successful coupling: When the DMPU was omitted, the reaction proceeded slowly. With diene **10** in hand, the azepine ring could be formed by subjecting **10** to Grubbs' second generation catalyst[7] (**G2**) in refluxing CH_2Cl_2 at high dilution (c = 0.005 M), which afforded the cyclized product **2** in excellent yield. When the reaction was run at higher concentrations (c > 0.01 M), the desired product was isolated along with inseparable dimerization byproducts.

Unfortunately, all attempts to install the C8-hydroxy group along with the correct C8−C9 *trans*-stereochemistry by treating β,γ-unsaturated ester **2** with a variety of hydroborating agents failed (Scheme 3). When using 9-BBN in THF at reflux,[8] no

(1) (a) Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571−576. (b) Pilli, R. A.; Ferreira de Oliveira, M. C. *Nat. Prod. Rep.* **2000**, *17*, 117−127 and references cited therein.

(2) Total and formal syntheses of (−)-stemoamide: (a) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417−6420. (b) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356−8357. (c) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295−4303. (d) Gurjar, M. K.; Reddy, D. S. *Tetrahedron Lett.* **2002**, *43*, 295−298. (e) Sibi, M. P.; Subramanian, T. *Synlett* **2004**, 1211−1214. (f) Olivo, H. F.; Tovar-Miranda, R.; Barragán, E. *J. Org. Chem.* **2006**, *71*, 3287−3290.

(3) Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2063−2070.

(4) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521−522.

(5) (a) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731−734. (b) Hodgson, D. M.; Foley, A. M.; Lovell, P. J. *Synlett* **1999**, 744−746.

(6) Roberts, C. D.; Schütz, R.; Leumann, C. J. *Synlett* **1999**, 819−821.

(7) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207.

(8) For hydroboration of trisubstituted β,γ-unsaturated amides using 9-BBN, see: Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1999**, *64*, 4790−4794.

10.1021/jo070498o CCC: $37.00
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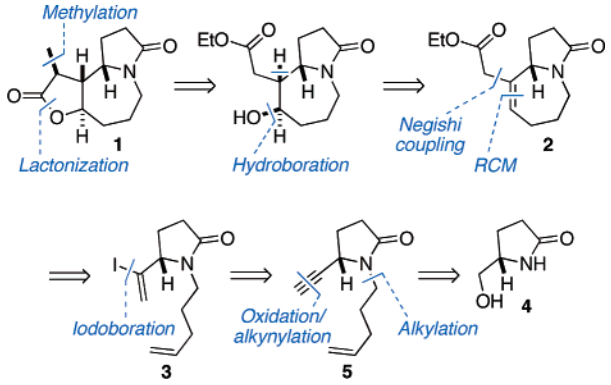
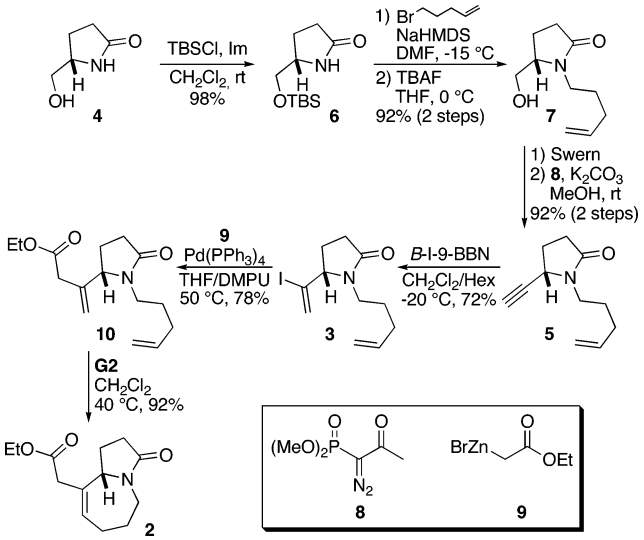
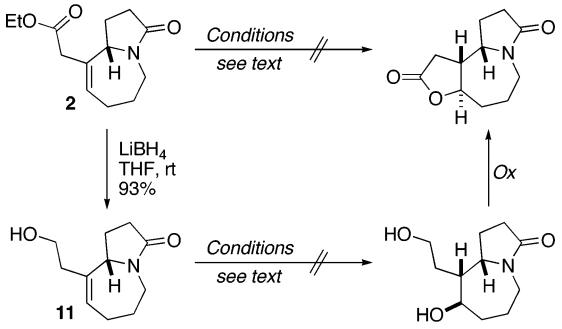
SCHEME 1. Retrosynthetic Analysis of (−)-Stemoamide



SCHEME 2. Construction of Pyrrolo[1,2-*a*]azepine Core



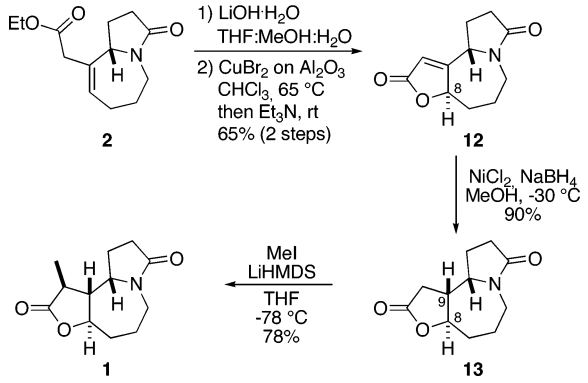
SCHEME 3. Failed Hydroboration Attempts



reaction occurred. Treatment of **2** with BH_3·THF at low temperature ($T < -25$ °C) gave no reaction, while increasing the reaction temperature gave a complex mixture of products. It is known that hydroboration of β,γ-unsaturated esters using BH_3·THF can lead to reduction of the ester moiety, furnishing the corresponding primary alcohol.[9] Therefore, in order to test the hydroboration reaction without the interfering ester reduction, **2** was reduced to alcohol **11** using $LiBH_4$ in excellent yield. Alcohol **11** was then subjected to the same hydroboration conditions, as well as Evans' catecholborane/SmI_3 procedure.[10]

(9) Simila, S. T. M.; Reichelt, A.; Martin, S. F. *Tetrahedron Lett.* **2006**, *47*, 2933−2936.

SCHEME 4. Bromolactonization and Endgame



In these cases, either no reaction occurred or the amide was reduced along with hydroboration of the olefin. It has been reported by others that hydroboration of hindered trisubstituted olefins in the presence of amides can be troublesome.[11]

To modify our synthetic strategy, we decided to install the butyrolactone moiety using a bromolactonization reaction, a strategy that was successfully used by Mori and co-workers in their efforts toward **1**.[2b]

Thus hydrolysis of ethyl ester **2** using LiOH gave the crude acid (Scheme 4), which upon exposure to $CuBr_2$ on alumina at 65 °C in $CHCl_3$ successfully gave the desired 5-*endo* cyclization product, which, followed by treatment with triethylamine at room temperature, effected elimination to butenolide **12** as a single diastereomer (65% yield from ester **2**).[2b,12] The formation of the C8 β-epimer in the bromolactonization was gratifying, although it was not easily predicted from molecular models. The same observations were made by Mori and co-workers. The C8−C9 *trans*-stereochemistry required for **1** was then introduced via a stereoselective 1,4-reduction of butenolide **12** from the sterically most accessible β-face using $NiCl_2$·$6H_2O$ and $NaBH_4$,[2b,c,e,13] which gave the known lactone **13** in high yield.[2e,f,3] Finally, α-methylation of lactone **13** under the reported conditions finished the synthesis of (−)-stemoamide.[2e,f,3] Analytical data for **1** were in all aspects identical with those reported in the literature.[2]

In conclusion, we have developed a 12-step, stereoselective total synthesis of (−)-stemoamide (**1**) in 20% overall yield starting from commercially available (*S*)-pyroglutaminol (**4**). The key features of the synthesis are (i) an iodoboration/Negishi/RCM sequence for the construction of β,γ-unsaturated azepine derivative **2** and (ii) a stereoselective bromolactonization/1,4-reduction strategy for the installation of the requisite C8−C9 *trans*-stereochemistry.

Experimental Section

For general experimental procedures, see Supporting Information.

(*S*)-5-(*tert*-Butyldimethylsilanyloxymethyl)pyrrolidin-2-one (6). To a solution of 1° alcohol **4** (1.000 g, 8.69 mmol) in CH_2Cl_2 (15 mL) and DMF (2 mL) was added TBSCl (1.570 g, 10.42 mmol) followed by imidazole (1.480 g, 21.71 mmol), and the resultant

(10) Evans, D. A.; Muci, A. R.; Stürmer, R. *J. Org. Chem.* **1993**, *58*, 5307−5309.

(11) Enders, D.; Lenzen, A.; Backes, M.; Janeck, C.; Catlin, K.; Lannou, M.-I.; Runsink, J.; Raabe, G. *J. Org. Chem.* **2005**, *70*, 10538−10551.

(12) Rood, G. A.; DeHaan, J. M.; Zibuck, R. *Tetrahedron Lett.* **1996**, *37*, 157−158.

(13) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817.

mixture was stirred for 3.5 h at rt and then quenched with H_2O. The phases were separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (heptane/EtOAc 1:2) of the residue gave **6** (1.944 g, 98%) as a clear oil: $[\alpha]^{20}_D$ 44.7 (*c* 1.8, $CHCl_3$); IR (film) 1692, 1463, 1255, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.96 (br s, 1H), 3.74 (ddd, J = 12.6, 7.8, 4.8 Hz, 1H), 3.61 (dd, J = 10.1, 4.0 Hz, 1H), 3.44 (dd, J = 10.1, 7.6 Hz, 1H), 2.33 (m, 2H), 2.16 (m, 1H), 1.73 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 66.9, 55.8, 29.8, 25.8, 22.7, 18.2, −5.46, −5.47; HRMS (ESI+) calcd for $C_{11}H_{24}NO_2Si$ $[M + H]^+$ 230.1571, found 230.1570.

(*S*)-5-(Hydroxymethyl)-1-(pent-4-enyl)pyrrolidin-2-one (7). To a solution of amide **6** (887 mg, 3.87 mmol), 5-bromopent-1-ene (920 μL, 7.73 mmol), and tetrabutylammonium iodide (143 mg, 0.387 mmol) in DMF (50 mL) was added dropwise NaHMDS (4.64 mL, 4.64 mmol, 1.0 M in THF) at −15 °C. The resultant mixture was stirred at −15 °C for 10 min, at rt for 3 h, and then quenched with saturated NH_4Cl (10 mL). The mixture was diluted with H_2O and extracted three times with CH_2Cl_2. The combined organic extracts were washed twice with H_2O and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the amide as a yellow oil (1.317 g). The residue was carried on to the next step directly. An analytically pure sample was obtained with flash chromatography (pentane/EtOAc 1:1): $[\alpha]^{20}_D$ 9.0 (*c* 1.5, $CHCl_3$); IR (film) 2955, 1671, 1422, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (tdd, J = 16.9, 10.2, 6.6 Hz, 1H), 4.98 (m, 2H), 3.62 (m, 4H), 3.00 (ddd, J = 13.9, 8.9, 5.2 Hz, 1H), 2.43 (ddd, J = 17.3, 9.5, 8.0 Hz, 1H), 2.28 (ddd, J = 16.8, 10.2, 4.9 Hz, 1H), 2.05 (m, 3H), 1.81 (m, 1H), 1.68 (m, 1H), 1.57 (m, 1H), 0.87 (s, 9H), 0.04 (d, J = 2.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 137.8, 115.0, 64.1, 59.1, 40.5, 31.1, 30.4, 26.6, 25.8, 21.5, 18.1, −5.6; HRMS (ESI+) calcd for $C_{16}H_{32}NO_2Si$ $[M + H]^+$ 298.2197, found 298.2208.

To a solution of the crude lactam (1.317 g) in THF (20 mL) was added TBAF (1.340 g, 4.25 mmol) in one portion at 0 °C. The resultant mixture was stirred at 0 °C for 1 h and then concentrated under reduced pressure. Flash chromatography (EtOAc → EtOAc + 4% MeOH) of the residue gave **7** (650 mg, 92% from **6**) as a clear oil: $[\alpha]^{20}_D$ 15.0 (*c* 0.3, $CHCl_3$); IR (film) 3344 (br), 2931, 1664, 1422, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (tdd, J = 16.9, 10.2, 6.6 Hz, 1H), 5.01 (m, 2H), 3.79 (m, 1H), 3.70 (td, J = 13.0, 4.3 Hz, 1H), 3.64 (m, 2H), 3.00 (ddd, J = 14.1, 9.1, 5.1 Hz, 1H), 2.47 (ddd, J = 17.3, 10.0, 7.3 Hz, 1H), 2.33 (ddd, J = 17.0, 10.2, 5.4 Hz, 1H), 2.10 (m, 3H), 1.95 (m, 1H), 1.83 (br s, 1H), 1.69 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 137.6, 115.2, 63.0, 58.9, 40.4, 31.1, 30.4, 26.6, 21.2; HRMS (ESI+) calcd for $C_{10}H_{18}NO_2$ $[M + H]^+$ 184.1332, found 184.1335.

(*S*)-5-Ethynyl-1-(pent-4-enyl)pyrrolidin-2-one (5). To a solution of DMSO (770 μL, 10.85 mmol) in CH_2Cl_2 (20 mL) was added oxalyl chloride (480 μL, 5.43 mmol) at −78 °C, and the mixture was stirred for 20 min. To this mixture was added alcohol **7** (663 mg, 3.62 mmol) in CH_2Cl_2 (10 mL) at −78 °C, and the resultant mixture was stirred for 2 h. Freshly distilled Et_3N (2.52 mL, 18.09 mmol) was then added. After 1 h, the mixture was allowed to warm to rt. The reaction was quenched with H_2O (6 mL) and brine (6 mL), and the phases were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The resultant crude aldehyde was used directly in the next step.

To a solution of crude aldehyde and K_2CO_3 (1.500 g, 10.85 mmol) in dry MeOH (20 mL) was added phosphonate **8** (1.040 g, 5.43 mmol) in dry MeOH (10 mL) at 0 °C. After the addition was complete, the mixture was allowed to reach rt. After 1 h at rt, the reaction mixture was diluted with Et_2O (30 mL), H_2O (10 mL), and brine (10 mL), and the phases were separated. The aqueous layer was extracted twice with Et_2O, and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (pentane/EtOAc 3:1 → 1:1) of the residue gave **5** (588 mg, 92% from **7**) as a clear oil: $[\alpha]^{20}_D$ −24.6 (*c* 1.0, $CHCl_3$); IR (film) 3295, 2928, 1688, 1416 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (tdd, J = 16.9, 10.2, 6.6 Hz, 1H), 5.00 (m, 2H), 4.32 (m, 1H), 3.63 (ddd, J = 13.8, 8.9, 7.0 Hz, 1H), 3.12 (ddd, J = 13.8, 8.3, 5.4 Hz, 1H), 2.50 (m, 1H), 2.40 (d, J = 2.1 Hz, 1H), 2.34 (m, 2H), 2.09 (m, 3H), 1.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 137.6, 115.1, 81.5, 73.3, 48.9, 40.6, 31.1, 29.9, 26.3, 26.3; HRMS (FAB+) calcd for $C_{11}H_{16}NO$ $[M + H]^+$ 178.1226, found 178.1232.

(*S*)-5-(1-Iodovinyl)-1-(pent-4-enyl)pyrrolidin-2-one (3). To a solution of alkyne **5** (30.0 mg, 0.169 mmol) in CH_2Cl_2/hexane (1:1, 2 mL) was added *B*-I-9-BBN[14] (508 μL, 0.508 mmol, 1.0 M in hexanes) dropwise at −20 °C. The resultant mixture was stirred at −20 °C for 17 h, then AcOH (540 μL) was added and the temperature was increased to 0 °C. After 70 min, NaOH (3.8 mL, 3M) and H_2O_2 (700 μL, 35 wt %) were added and the mixture was warmed to rt. After 1.5 h, the reaction mixture was diluted with H_2O (1 mL) and the phases were separated. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (pentane/EtOAc 2:1) of the residue gave **3** (37.2 mg, 72%) as a pale yellow oil: $[\alpha]^{20}_D$ 20.8 (*c* 0.4, $CHCl_3$); IR (film) 2932, 1680, 1419, 915 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.36 (d, J = 1.8 Hz, 1H), 5.92 (d, J = 1.9 Hz, 1H), 5.79 (tdd, J = 16.9, 10.2, 6.6 Hz, 1H), 5.01 (m, 2H), 3.89 (dd, J = 8.7, 3.8 Hz, 1H), 3.69 (ddd, J = 13.9, 8.9, 7.1 Hz, 1H), 2.74 (ddd, J = 14.0, 8.4, 5.4 Hz, 1H), 2.58 (ddd, J = 17.3, 10.4, 7.1 Hz, 1H), 2.36 (ddd, J = 17.1, 10.6, 5.2 Hz, 1H), 2.17 (m, 1H), 2.05 (m, 2H), 1.86 (m, 1H), 1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 137.6, 127.7, 116.0, 115.1, 66.9, 40.2, 31.1, 29.4, 26.1, 24.7; HRMS (ESI+) calcd for $C_{11}H_{17}INO$ $[M + H]^+$ 306.0349, found 306.0344.

Ethyl 3-((*S*)-5-Oxo-1-(pent-4-enyl)pyrrolidin-2-yl)but-3-enoate (10). To a solution of vinyliodide **3** (102.0 mg, 0.334 mmol) and $Pd(PPh_3)_4$ (38.6 mg, 0.0334 mmol) in THF/DMPU (3:1, 5.5 mL) was added Reformatsky reagent **9** (1.240 mL, 0.668 mmol, c < 0.54 M)[6] at 50 °C. The resultant mixture was stirred at 50 °C for 50 min and then quenched with saturated NH_4Cl (2 mL) and poured into Et_2O/H_2O. The phases were separated, and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (pentane/EtOAc 1:1) of the residue gave **10** (69.7 mg, 78%) as a clear oil: $[\alpha]^{20}_D$ 22.3 (*c* 0.4, $CHCl_3$); IR (film) 1729, 1675, 1522, 1422 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (tdd, J = 16.9, 10.2, 6.6 Hz, 1H), 5.14 (s, 1H), 5.07 (s, 1H), 4.98 (m, 2H), 4.18 (dd, J = 8.7, 3.7 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.66 (ddd, J = 13.7, 8.8, 7.2 Hz, 1H), 3.00 (dd, J_{ABX} = 15.5, 0.6 Hz, 1H), 2.95 (dd, J_{ABX} = 15.5, 0.9 Hz, 1H), 2.72 (ddd, J = 13.8, 8.5, 5.5 Hz, 1H), 2.44 (m, 1H), 2.33 (ddd, J = 16.9, 9.8, 4.6 Hz, 1H), 2.20 (m, 1H), 2.03 (m, 2H), 1.79 (m, 1H), 1.57 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 170.8, 140.5, 137.7, 116.0, 114.99, 114.96, 62.2, 61.0, 40.2, 37.5, 31.1, 29.6, 26.2, 23.8, 14.1; HRMS (ESI+) calcd for $C_{15}H_{24}NO_3$ $[M + H]^+$ 266.1751, found 266.1750.

β,γ-Unsaturated Ester 2. To a solution of diene **10** (50.0 mg, 0.188 mmol) in CH_2Cl_2 (37 mL) was added Grubbs' second generation catalyst (8.0 mg, 0.0094 mmol) in CH_2Cl_2 (1 mL) at reflux. The resultant mixture was refluxed for 3.5 h and then concentrated under reduced pressure. Flash chromatography (pentane/EtOAc 1:3 → 1:5) of the residue gave **2** (41.3 mg, 92%) as a clear oil: $[\alpha]^{20}_D$ −78.7 (*c* 1.2, $CHCl_3$); IR (film) 1730, 1681, 1420, 1266, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.66 (dd, J = 8.4, 5.4 Hz, 1H), 4.21 (dt, J = 7.5, 1.3 Hz, 1H), 4.13 (dq, J = 7.1, 1.2 Hz, 2H), 4.04 (ddd, J = 13.7, 8.0, 3.7 Hz, 1H), 2.96 (m, 3H), 2.40 (m, 2H), 2.27 (m, 2H), 1.97 (m, 2H), 1.85 (m, 1H), 1.71 (m,

(14) Commercial grade, freshly opened bottle.

1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 171.4, 134.4, 129.0, 63.5, 60.8, 40.8, 39.4, 30.4, 25.6, 24.8, 22.7, 14.2; HRMS (ESI+) calcd for $C_{13}H_{20}NO_3$ $[M + H]^+$ 238.1438, found 238.1442.

Butenolide 12. To a solution of ester **2** (110 mg, 0.463 mmol) in THF/MeOH/H_2O (18 mL, 2:1:1) was added LiOH·H_2O (39 mg, 0.927 mmol). The resultant mixture was stirred for 2 h at rt and then acidified with HCl (5.5 mL, 1 M) and extracted five times with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude acid (106 mg) as a white solid, which was used directly in the next step.

To a solution of the crude acid (106 mg) in $CHCl_3$ (46 mL) was added $CuBr_2$ on Al_2O_3 (1.570 g, 2.315 mmol).[15] The resultant heterogeneous solution was heated to 65 °C in a preheated oil bath for 4 h. The reaction mixture was then cooled to rt, Et_3N (320 μL, 2.315 mmol) was added, and the stirring was continued for 3 h. The reaction mixture was filtered, and the solid was washed with MeOH followed by concentration of the filtrate under reduced pressure. The residue was dissolved in water and extracted five times with EtOAc, dried ($MgSO_4$), and concentrated. Flash chromatography (4% MeOH in CH_2Cl_2) of the residue gave **12** (62 mg, 65% from **2**) as a white solid: mp 157−158 °C; $[\alpha]^{20}_D$ −224.0 (*c* 0.4, $CHCl_3$); IR (film) 2930, 1756, 1689, 1522, 1429 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (t, J = 1.4 Hz, 1H), 4.99 (m, 1H), 4.77 (tt, J = 8.1, 1.2 Hz, 1H), 4.27 (m, 1H), 2.48 (m, 5H), 1.85 (m, 2H), 1.69 (m, 1H), 1.41 (ddt, J = 13.4, 11.8, 3.5, Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 174.0, 171.6, 115.8, 82.8, 58.1, 43.3, 34.4, 30.1, 27.6, 25.6; HRMS (FAB+) calcd for $C_{11}H_{14}NO_3$ $[M + H]^+$ 208.0968, found 208.0972.

Lactone 13. To a solution of butenolide **12** (24.0 mg, 116 μmol) in MeOH (2.0 mL) was added $NiCl_2$·$6H_2O$ (6.9 mg, 29 μmol) followed by $NaBH_4$ (17.5 mg, 463 μmol) at −30 °C. After 3 h, the solution was quenched with HCl (1.0 mL, 1 M) and diluted with CH_2Cl_2 (3 mL). The phases were separated, and the aqueous layer was extracted three times with CH_2Cl_2, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (2 → 4% MeOH in CH_2Cl_2) of the residue gave **13** (21.7 mg, 90%) as a clear oil: $[\alpha]^{20}_D$ −94.0 (*c* 0.4, $CHCl_3$) [lit. $[\alpha]^{25}_D$ −144 (*c* 1.0, $CHCl_3$)[2e]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (dt, J = 10.2, 3.0 Hz, 1H), 4.16 (m, 1H), 3.99 (td, J = 10.6, 6.4 Hz, 1H), 2.85 (m, 1H), 2.68 (m, 1H), 2.65 (dd, J = 17.4, 8.8 Hz, 1H), 2.51 (dd, J = 17.3, 12.7 Hz, 1H), 2.45−2.35 (m, 3H), 2.07 (m, 1H), 1.91−1.85 (m, 1H), 1.71 (quint, J = 10.7 Hz, 1H), 1.59−1.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 174.0, 79.8, 56.0, 44.9, 40.2, 34.6, 31.0, 30.6, 25.5, 22.7.

(−)-Stemoamide (1). To a solution of lactone **13** (8.2 mg, 39.2 μmol) in THF (0.5 mL) was added LiHMDS (43 μL, 43.1 μmol, 1.0 M in toluene) at −78 °C. After 10 min, the reaction flask was placed in a 0 °C ice bath for 5 min and then recooled to −78 °C. MeI (12.2 μL, 196 μmol) was added, and stirring was continued for 3 h at −78 °C after which the mixture was allowed to reach rt. The reaction was quenched with saturated NH_4Cl (0.5 mL), extracted four times with EtOAc, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (3% MeOH in CH_2Cl_2) of the residue gave **1** (6.8 mg, 78%) as a white solid: mp 182−183 °C; $[\alpha]^{20}_D$ −141 (*c* 0.3, MeOH) [lit. $[\alpha]^{26}_D$ −141 (*c* 0.19, MeOH),[2a] $[\alpha]^{26}_D$ −181 (*c* 0.89, MeOH),[2a] $[\alpha]^{30}_D$ −219.3 (*c* 0.5, MeOH),[2b] $[\alpha]^{25}_D$ −183.5 (*c* 1.36, MeOH),[2c] $[\alpha]^{25}_D$ −187 (*c* 0.5, MeOH)[2f]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (m, 2H), 3.99 (dt, J = 10.8, 6.4 Hz, 1H), 2.69−2.56 (m, 2H), 2.45−2.38 (m, 4H), 2.08−2.02 (m, 1H), 1.89−1.84 (m, 1H), 1.71 (dq, J = 12.2, 10.7 Hz, 1H), 1.59−1.50 (m, 2H), 1.31 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 174.0, 77.6, 55.8, 52.7, 40.2, 37.3, 34.8, 30.6, 25.6, 22.6, 14.1.

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Supporting Information Available: General experimental procedures and ^{1}H and ^{13}C NMR spectra for compounds **1**−**3**, **5**−**7**, **10**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For the preparation of $CuBr_2$ on Al_2O_3, see: Kodomari, M.; Satoh, H.; Yoshitomi, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4149−4150.