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Synthesis of (−)-Stemoamide Using a Stereoselective *anti*-Aldol Step

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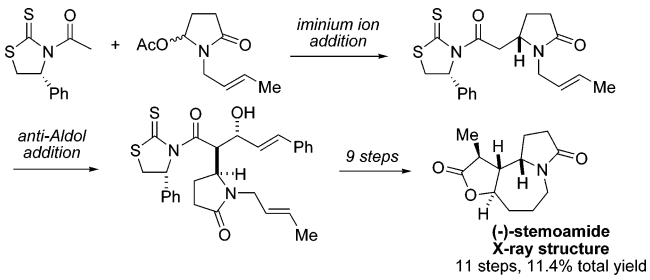
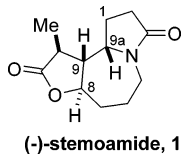


The synthesis of (−)-stemoamide was achieved in 11 steps from 5-acetoxy-*N*-crotyl pyrrolidinone. A chiral *N*-acyl thiazolidinethione was employed in a stereoselective addition to a cyclic *N*-acyl iminium ion to install the required stereochemistry of carbon C9a. This iminium ion addition product was employed in a stereoselective $MgBr_2$-catalyzed *anti*-aldol reaction to install the required stereochemistry of carbons C8 and C9. The X-ray crystal analysis of (−)-stemoamide confirmed the structure and the stereochemical outcome of these selective reactions.

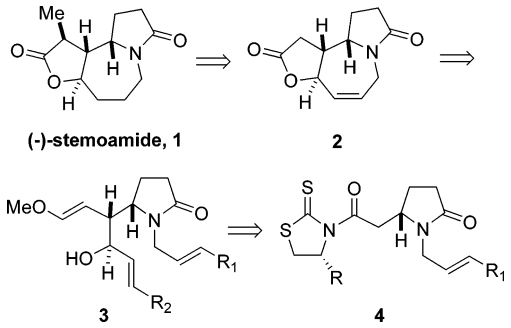
The *Stemonaceae* plant family is a rich source of bioactive alkaloids with more than 70 alkaloids isolated to date.[1] The rhizomes and root extracts of these plants have been used in traditional Chinese and Japanese folk medicine as insecticides, as vermifuges, and also for the treatment of respiratory diseases such as bronchitis, pertussis, and tuberculosis. (−)-Stemoamide (**1**) was isolated from the roots and rhizomes of *Stemona tuberosa* by Xu et al., in 1992.[2] Stemoamide is one of the structurally simplest members of the *Stemona* family possessing a γ-lactone fused to a pyrrolo[1,2*a*]azepine nucleus. Several syntheses of racemic and natural stemoamide have been achieved to date[3,4] as well as have several approaches to the tricyclic core.[5] With the exception of Jacobi's seven-step synthesis of stemoamide,[3d,4b] syntheses of stemoamide either are too long or lack a complete stereochemical control during the installation of the contiguous stereocenters and consequently require extra steps to correct their stereochemistry. As part of our program in the synthesis and pharmacology of *Stemona* alkaloids with unique biological properties,[6] we sought to develop enantioselective strategies which will allow us to prepare large amounts of these alkaloids. As a first step toward this goal, we embarked on a practical synthesis of (−)-stemoamide.



(-)-stemoamide, 1

We envisioned a synthetic strategy of (−)-stemoamide that relied on installing the correct stereochemistry of the three contiguous stereocenters C8, C9, and C9a employing a chiral thiazolidinethione as illustrated in Scheme 1. Conversion of the

SCHEME 1. Retrosynthetic Analysis of (−)-Stemoamide



hydrogenated product of **2** to stemoamide is well precedented.[3f,4a] The lactone ring would be prepared from Wittig olefination product **3**, and the azepine ring would be formed by a ring-closing olefin metathesis (RCM). Installing the correct stereochemistry of C8 and C9 would require an *anti*-aldol reaction of *N*-acyl thiazolidinethione **4**, and introducing the stereochemistry of C9a would require the addition of a chiral *N*-acetylimide to a cyclic iminium ion.

We recently reported the stereoselective addition of the titanium(IV) enolate of *N*-acetyl-4*S*-isopropylthiazolidinethiones to cyclic *N*-acyl iminium ions.[7] Addition of a metal enolate derived from *N*-acetyl thiazolidinethione to a cyclic *N*-acyl imine creates a stereocenter with stereochemistry opposite of the one

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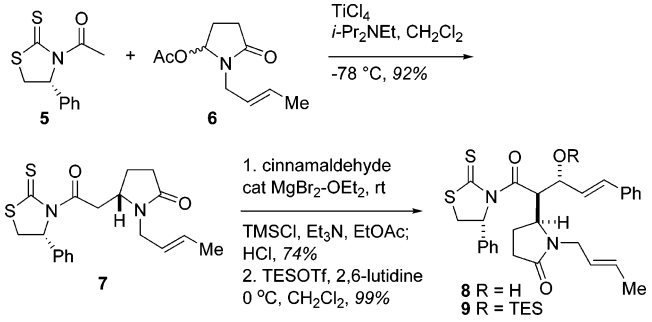
SCHEME 2. Chiral Thiazolidinethione-Directed Addition to Iminium Ion and *anti*-Aldol



obtained when added to an *N*-acyl iminium ion using the same chiral auxiliary.[8,9] Because *N*-acetyl-4*R*-isopropylthiazolidinethione would be too costly to prepare, we selected the 4*R*-phenyl thiazolidinethione **5** for the construction of the required stereochemistry of C9a as found in natural stemoamide (Scheme 2). Addition of the titanium enolate of **5** to the iminium ion formed from 5-acetoxy pyrrolidinone **6**[10] gave the desired diastereomeric product **7** in 92% isolated yield after column chromatography.

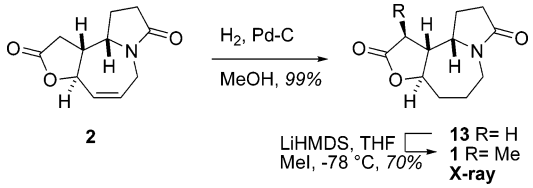
A highly diastereoselective *anti*-aldol reaction employing chiral thiazolidinethione auxiliaries was recently disclosed by Evans.[11] The reaction is catalytic in magnesium salts and is facilitated by silylation with chlorotrimethylsilane at room temperature. We reported this *anti*-aldol reaction when the aldehyde employed was cinnamaldehyde and the *N*-acyl thiazolidinethione was the addition product of the titanium(IV) enolate of *N*-acetyl-4*S*-isopropylthiazolidinethione with *N*-crotyl-5-acetoxy pyrrolidinone.[7] An X-ray crystallographic analysis confirmed the stereochemical output of the reaction. When thiazolidinethione **7** was employed in the *anti*-aldol reaction with acrolein, no reaction was observed. However, when the aldehyde employed was cinnamaldehyde, aldol product **8** was obtained in 74% yield after column chromatography (Scheme 2). Because the reactions were carried out with the 4*S*-substituted thiazolidinethione instead of with the 4*R*-isomer, as previously described,[7] we presumed aldol product **8** had a stereochemistry opposite of the product obtained when using the 4*R*-isomer. Thus, aldol product **8** possesses the required stereochemistry of carbons C8, C9, and C9a for the synthesis of (−)-stemoamide. Aldol product **8** was protected as the triethylsilyl ether **9** in quantitative yield.

Homologation of the acyl group of **9** to form the γ-lactone and RCM to form the azepine ring are illustrated in Scheme 3. Although many chiral thiazolidinethiones can be reduced directly to the corresponding aldehyde,[12] we were unable to partially reduce thiazolidinethione **9** to aldehyde **11** in good yields. However, reduction of thiazolidinethione with sodium borohydride occurred in 96% yield, and oxidation of the alcohol **10** to aldehyde **11** occurred in 90% yield.

Aldehyde **11** was reacted with the phosphonium salt $Ph_3P^+CH_2OCH_3Cl^-$ in the presence of NaHMDS to give an inseparable *E*,*Z*-mixture of methylvinyl ethers; under acidic conditions, the silyl ether was removed and the methylvinyl ether was hydrolyzed to deliver a diastereomeric mixture of lactols in 88% yield. Oxidation of the lactols with PCC gave the desired lactone **12** in very good yield. Although many combinations of dienes have been reported in ring-closing olefin metathesis (RCM), we found no RCM literature precedent with vinylic methyl and phenyl groups.[13] We found that RCM using the second generation of Grubbs' catalyst (Grubbs II) in refluxing 1,2-dichloroethane furnished azepine **2** in 60% yield.

The two remaining steps to complete the total synthesis are illustrated in Scheme 4. Palladium-catalyzed hydrogenation of

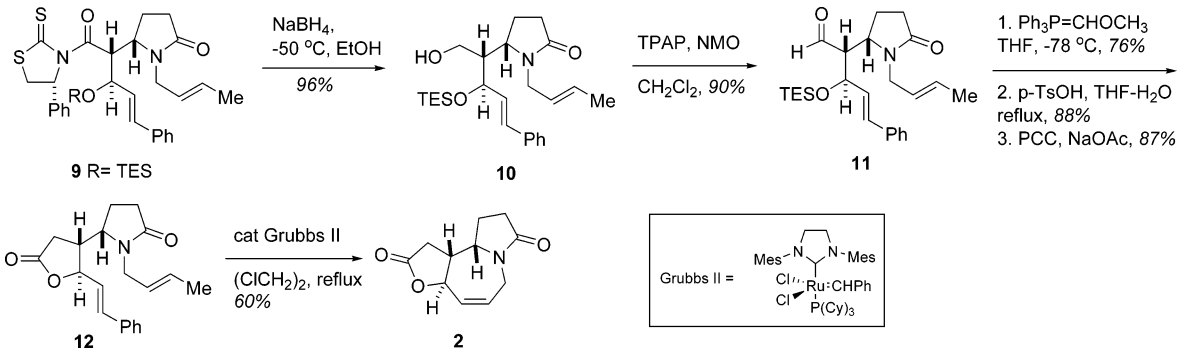
SCHEME 4. Completion of the Synthesis



the unsaturated azepine **2** gave compound **13** in almost quantitative yield. Stereoselective methylation of C10 on the less-hindered face of lactone **13** at low temperature gave stemoamide **1** in 70% yield, as previously reported by Narasaka[4a] and Sibi.[3f] All spectroscopic data and physical data of stemoamide were in agreement with the published data.[2,3] The X-ray crystallographic analysis of (−)-stemoamide confirmed the stereochemistry of the product as envisioned in the synthetic plan.

In summary, we have achieved a synthesis of (−)-stemoamide in 11 steps starting from easily prepared starting materials (14% overall yield). We have demonstrated the utility of the stereoselective addition of a titanium(IV) enolate of *N*-acetyl thiazolidinethione to a cyclic iminium ion and the use of the same chiral auxiliary to control the stereochemistry in a $MgBr_2$-catalyzed *anti*-aldol reaction for the synthesis of (−)-stemoamide. The structure of (−)-stemoamide was confirmed by X-ray crystallographic analysis.

SCHEME 3. Homologation and Azepine Construction



Experimental Section

(−)-5(*S*)-[2-(4(*R*)-Phenyl-2-thioxo-thiazolidine-3-yl)-2-oxo-ethyl]-1-(but-2-enyl)-pyrrolidine-2-one 7. A solution of $TiCl_4$ (1 M in CH_2Cl_2, 1.5 mL, 1.5 mmol) was added to a solution of *N*-acetyl-4(*R*)-phenyl thiazolidinethione (356 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C. The solution was stirred for 5 min and then cooled to −30 °C. The reaction mixture was treated with a solution of diisopropylethylamine (220 mg, 1.7 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 40 min and cooled to −78 °C. A solution of 5-acetoxy *N*-crotyl pyrrolidine-2-one (395 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was added to the reaction mixture via cannula. The reaction mixture was stirred and warmed to 0 °C for 6 h. The reaction was quenched by addition of saturated NH_4Cl solution and stirred for 5 min. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was then washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by silica gel column chromatography ($CHCl_3$−EtOAc−petroleum ether, 4:2:1) to afford 516 mg of **7** as a yellow oil (92% yield): R_f 0.35 ($CHCl_3$−EtOAc−Petroleum Ether, 4:2:1); $[\alpha]_D^{25} = -359$ (*c* 1.0, $CHCl_3$); IR 3002, 1683, 1377, 1332, 1259, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44−7.33 (5H, m), 6.22 (1H, d, J = 8.2 Hz), 5.57 (1H, dq, J = 15.2, 6.4 Hz), 5.32 (1H, m), 4.07 (2H, bs), 3.96 (1H, dd, J = 11.3, 8.3 Hz), 3.90 (1H, dd, J = 17.6, 3.3 Hz), 3.52 (1H, dd, J = 15.2, 7.0 Hz), 3.16 (1H, dd, J = 17.5, 9.8 Hz), 3.09 (1H, dd, J = 10.4, 1.5 Hz), 2.48−2.17 (3H, m), 1.66 (3H, d, J = 6.4 Hz), 1.63 (1H, m); ^{13}C NMR ($CDCl_3$) δ 202.4 (C), 174.7 (C), 170.9 (C), 139.1 (C), 129.5 (CH), 129.3 (2CH), 128.9 (CH), 125.6 (2CH), 125.4 (CH), 69.7 (CH), 54.3 (CH), 42.7 ($2CH_2$), 36.6 (CH_2), 29.7 (CH_2), 24.6 (CH_2), 17.7 (CH_3).

1-(4*R*-Phenyl-2-thioxo-1,3-thiazolidin-3-yl)-(2*S*,3*R*)-3-hydroxy-2-(1-but-2-enyl-5-oxo-pyrrolidin-2(*S*)-yl)-5-phenyl-pent-4-en-1-one 8. To a solution of compound **7** (748 mg, 2 mmol) in ethyl acetate (6 mL) was added $MgBr_2{\cdot}OEt_2$ (78 mg, 0.3 mmol), cinnamaldehyde (0.278 mL, 2.2 mmol), triethylamine (0.558 mL, 4 mmol), and TMSCl (0.381 mL, 3 mmol). The mixture was stirred at room temperature for 36 h. The reaction was filtered through a plug of silica and eluted with ethyl acetate. The eluent was concentrated in vacuo, and the residue was dissolved in 20 mL of THF and 5 mL of 1 N HCl. After stirring for 1h at room temperature, the mixture was diluted with 100 mL of AcOEt and 100 mL of water. The phases were separated, and the organic layer was washed with a saturated solution of $NaHCO_3$ (2 × 30 mL) and brine (2 × 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with petroleum ether−acetone (7:3, 6:4, 5:5, and 4:6): 772 mg (74% yield); R_f 0.32 (4:2:1, chloroform−ethyl acetate−petroleum ether); $[\alpha]_D^{25} = -331$ (*c* 1.0, $CHCl_3$); IR 3345, 2937, 1669, 1449, 1256, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43−7.24 (10H, m), 6.64 (1H, dd, J = 16.0, 1.7 Hz), 6.23 (1H, dd, J = 16.0, 4.0 Hz), 5.95 (1H, d, J = 7.8 Hz), 5.33 (1H, m), 5.32 (1H, dd, J = 6.8, 3.6 Hz), 5.21 (1H, m), 4.63 (1H, bs), 4.29 (1H, m), 4.17 (1H, dd, J = 15.2, 5.6 Hz), 3.38 (1H, dd, J = 11.2, 8.1 Hz), 3.23 (1H, dd, J = 15.2, 6.6 Hz), 2.94 (1H, dd, J = 11.2 Hz), 2.60 (1H, dt, J = 17.0, 9.2 Hz), 2.30 (1H, dd, J = 9.7, 3.5 Hz), 2.01 (1H, m), 1.66 (1H, m), 1.58 (3H, d, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (CS), 175.6 (CO), 174.3 (CO), 138.8 (C), 136.2 (C), 130.0 (CH), 129.8 (CH), 129.6 (CH), 129.3 (2CH), 129.0 (CH), 128.9 (CH), 128.3 (CH), 126.5 (2CH), 125.6 (2CH), 124.9 (CH), 70.5 (CH), 70.2 (CH), 56.9 (CH), 50.4 (CH), 43.1 (CH_2), 36.7 (CH_2), 30.1 (CH_2), 21.8 (CH_2), 17.9 (CH_3).

TES-Protected Aldol Product 9. To a dichloromethane solution cooled to −50 °C was added TESOTf (0.2 mL, 0.89 mmol) and 2,6-lutidine (0.1 mL, 0.89 mmol). After the solution was stirred for 15 min, the alcohol **8** dissolved in dichloromethane was added via cannula. The reaction mixture was warmed to room temperature overnight. The solution was washed with saturated Na_2CO_3. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 7:3) to give 366 mg (99%). R_f 0.34 (7:3, petroleum ether−ethyl acetate); $[\alpha]_D^{25} = -286$ (*c* 1.0, $CHCl_3$); IR 2955, 2911, 1690, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41−7.22 (10H, m), 6.55 (1H, d, J = 15.9 Hz), 6.16 (1H, dd, J = 15.8, 7.2 Hz), 6.08 (1H, d, J = 7.9 Hz), 5.52 (1H, m), 5.48 (1H, dq, J = 6.9, 4.9 Hz), 5.24 (1H, m), 4.68 (1H, t, J = 7.1 Hz), 4.14 (2H, m), 3.74 (1H, dd, J = 11.3, 8.0 Hz), 3.22 (1H, dd, J = 15.3, 7.2 Hz), 3.01 (1H, d, J = 11.3 Hz), 2.28 (3H, m), 1.98 (1H, m), 1.62 (3H, d, J = 6.3 Hz), 0.96 (9H, t, J = 8 Hz), 0.62 (6H, q, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 203.1 (C), 175.3 (C), 172.7 (C), 139.1 (C), 136.2 (C), 131.6 (CH), 129.9 (CH), 129.2 (CH), 129.1 (2CH), 128.9 (2CH), 128.6 (CH), 128.2 (CH), 126.7 (2CH), 125.4 (2CH), 125.3 (CH), 73.3 (CH), 70. 4 (CH), 56.0 (CH), 52.1 (CH), 43.0 (CH_2), 37.1 (CH_2), 30.4 (CH_2), 21.1 (CH_2), 17.9 (CH_3), 7.0 ($3CH_3$), 5.3 ($3CH_2$).

Alcohol 10. To a solution of thiazolidinethione **9** (257 mg, 0.414 mmol) in dry ethanol (4 mL) cooled to −15 °C was added $NaBH_4$ (32 mg, 0.86 mmol). The reaction was stirred at 4 °C overnight. Excess borohydride was quenched at 0 °C with diluted HCl and concentrated. The residue was partitioned between water and ether, and the organic layer was separated and washed with saturated Na_2CO_3 and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 7:3) to give 177 mg of **10** (96%) as a colorless oil: R_f 0.22 (1:1, petroleum ether−ethyl acetate); $[\alpha]_D^{25} = -17$ (*c* 1.0, $CHCl_3$); IR 3405, 2955, 1668, 1449, 1422 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39−7.24 (5H, m), 6.50 (1H, d, J = 15.9 Hz), 6.28 (1H, dd, J = 15.9, 6.5 Hz), 5.61 (1H, dq, J = 15.3, 6.5 Hz), 5.35 (1H, m), 4.54 (1H, dd, J = 7.6, 3.2 Hz), 4.40 (1H, ddt, J = 15.0, 4.9, 1.5 Hz), 3.99−3.89 (2H, m), 3.78 (1H, m), 3.44 (1H, dd, J = 15.0, 7.8 Hz), 3.11 (1H, bs), 2.45 (1H, m), 2.35 (1H, m), 2.24−2.08 (2H, m), 1.86 (1H, m), 1.66 (3H, d, J = 6.5 Hz), 0.96 (9H, t, J = 8.0 Hz), 0.62 (6H, q, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 175.7 (C), 136.3 (C), 131.2 (CH), 131.0 (CH), 129.6 (CH), 128.9 (2CH), 128.2 (CH), 126.7 (2CH), 125.5 (CH), 74.6 (CH), 61.5 (CH_2), 57.1 (CH), 48.1 (CH), 43.4 (CH_2), 30.4 (CH_2), 22.5 (CH_2), 17.9 (CH_3), 6.9 ($3CH_3$), 5.2 ($3CH_2$).

Aldehyde 11. To a solution of alcohol **10** (95 mg, 0.22 mmol) in 9.5 mL of DCM was added molecular sieves (170 mg), 4-methylmorpholine *N*-oxide (47 mg, 0.4 mmol), and TPAP (7 mg, 0.02 mmol). The mixture was stirred at room temperature and followed by TLC. After 1 h, the reaction was completed and it was filtered through a short column of silica gel and eluted with acetone to give 85 mg (90%) of aldehyde **11**: R_f 0.5 (1:1, petroleum ether−ethyl acetate); $[\alpha]_D^{25} = -90.8$ (*c* 1.0, $CHCl_3$); IR 2954, 2361, 1690, 1454, 1418, 1244 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.00 (1H, d, J = 1.6 Hz), 7.40−7.25 (5H, m), 6.56 (1H, d, J = 15.8 Hz), 6.34 (1H, dd, J = 15.8, 8.1 Hz), 5.59 (1H, dq, J = 15.3, 6.4

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Hz), 5.33 (1H, m), 4.67 (1H, dd, J = 8.2, 3.3 Hz), 4.31 (1H, ddt, J = 15.2, 5.3, 1.5 Hz), 4.20 (1H, dd, J = 11.6, 6.6 Hz), 3.30 (1H, dd, J = 15.2, 7.6 Hz), 2.75 (1H, m), 2.56−2.31 (2H, m), 2.24−2.16 (2H, m), 1.66 (3H, dd, J = 6.5, 0.9 Hz), 0.93 (9H, t, J = 8.0 Hz), 0.60 (6H, q, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 201.8 (CH), 175.5 (C), 135.8 (C), 132.0 (CH), 130.0 (CH), 129.8 (CH), 128.9 (2CH), 128.4 (CH), 126.7 (2CH), 125.1 (CH), 71.6 (CH), 59.4 (CH), 55.8 (CH), 43.2 (CH_2), 30.2 (CH_2), 21.4 (CH_2), 17.8 (CH_3), 6.9 ($3CH_3$), 5.3 ($3CH_2$).

Lactone 12. To a suspension of $MeOCH_2PPh_3Cl$ (1.100 g, 3.2 mmol) in dry THF (10 mL) at −78 °C was added NaHMDS (1 M in THF, 2.68 mL, 2.68 mmol) dropwise, and the mixture was stirred for 20 min. Aldehyde **11** (458 mg, 1.071 mmol) in dry THF (1 mL) was added dropwise to the reaction mixture. The reaction was stirred for 3 h at −78 °C and then allowed to warm to room temperature. The reaction was quenched with NH_4Cl (saturated, 5 mL), and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 3:2) to yield the Wittig product as a mixture of geometric isomers (371 mg, 76%). The Wittig product (334 mg, 0.733 mmol) was dissolved in THF−H_2O (16 mL, 3:1), and *p*-TsOH (140 mg, 0.733 mmol) was added. The mixture was refluxed for 4 h. The reaction was allowed to cool to room temperature and treated with $NaHCO_3$. The reaction mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/acetone, 6:4) to give 210 mg of a mixture of lactols (88%) as colorless oil. To a solution of lactols (200 mg, 0.61 mmol) in dichloromethane (60 mL) was added PCC (263 mg, 1.22 mmol) and sodium acetate (132 mg, 1.6 mmol). The mixture was stirred for 6 h at room temperature. The reaction was diluted with AcOEt (20 mL), filtered on a small column of silica gel (5 cm), and washed with dichloromethane. The solvent was evaporated to give lactone **12** (173 mg, 87%): R_f 0.43 (petroleum ether−ethyl acetate, 1:4); $[\alpha]_D^{25}$ = +70.1 (c 1.0, $CHCl_3$); IR 3025, 2928, 1777, 1684, 1424, 1171, 971 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40−7.28 (5H, m), 6.64 (1H, d, J = 15.8 Hz), 6.11 (1H, dd, J = 15.8, 7.0 Hz), 5.64 (1H, dq, J = 15.3, 6.4 Hz), 5.33 (1H, m), 4.89 (1H, dd, J = 7.1, 3.3 Hz), 4.34 (1H, d, J = 15.3 Hz), 3.84 (1H, m), 3.34 (1H, dd, J = 15.2, 7.6 Hz), 2.89−2.77 (2H, m), 2.57−2.32 (3H, m), 2.24−2.11 (1H, m), 1.89−1.77 (1H, m), 1.67 (3H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 175.4 (C), 175.2 (C), 135.4 (C), 133.9 (CH), 130.3 (CH), 128.9 (2CH), 128.3 (CH), 127.0 (2CH), 125.6 (CH), 125.1 (CH), 80.5 (CH), 58.2 (CH), 43.2 (CH_2), 42.1 (CH), 31.0 (CH_2), 30.1 (CH_2), 20.1 (CH_2), 17.9 (CH_3).

RCM Product 2. To a solution of diene **12** (26 mg, 80 μmol) in ethylene dichloride (10 mL) was added Grubb's catalyst second generation (6.8 mg, 8 μmol) dissolved in ethylene dichloride (6 mL) over 5 h. The reaction mixture was stirred at 110 °C for 20 h. The reaction was filtered on a plug of silica gel using acetone as solvent. The solvent was evaporated, and the residue was purified by column chromatography (methanol−dichloromethane, 5:95) to give metathesis product **2** (10 mg, 60%): R_f 0.29 (methanol−dichloromethane, 5:95); IR 3456, 2920, 1783, 1683, 1418, 1276, 1183, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.93 (1H, d, J = 11.3 Hz), 5.76 (1H, dddd, J = 11.3, 6.0, 2.3, 1.8 Hz), 5.03 (1H, dq, J = 10.5, 1.7 Hz), 4.74 (1H, dd, J = 18.4, 6.0 Hz), 4.10 (1H, dt, J = 9.8, 6.6 Hz), 3.45 (1H, bd, J = 18.4 Hz), 3.13 (1H, m), 2.70−2.46 (4H, m), 2.12 (1H, m), 2.12 (1H, m), 1.77 (1H, m); ^{13}C NMR ($CDCl_3$) δ 175.5 (C), 173.9 (C), 129.4 (CH), 128.6 (CH), 78.1 (CH), 57.0 (CH), 44.9 (CH), 40.7 (CH_2), 31.1 (CH_2), 30.9 (CH_2), 21.2 (CH_2); m/e calcd for $C_{11}H_{14}NO_3$ 208.0974, found 208.0969.

Desmethylstemoamide 13. To a solution of olefin **2** (52 mg, 80 μmol) in methanol (4 mL) was added 10% Pd−C (6 mg). The suspension was stirred overnight under H_2 atmosphere. The reaction was filtered through a small bed of Celite, and the solvent was evaporated to give desmethylstemoamide **13** (50 mg, 99%): R_f 0.26 (methanol−dichloromethane, 5:95); $[\alpha]_D^{25}$ = −144 (c 1.0, $CHCl_3$); IR 2931, 1776, 1671, 1420, 1185 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.29 (1H, dt, J = 10.4, 3.0 Hz), 4.15 (1H, dt, J = 14.0, 2.1 Hz), 4.00 (1H, dt, J = 10.7, 6.6 Hz), 2.92−2.80 (1H, m), 2.77−2.63 (1H, m), 2.65 (1H, dd, J = 17.4, 8.5 Hz), 2.46−2.36 (4H, m), 2.13−2.03 (1H, m), 1.90−1.84 (1H, m), 1.72 (1H, quin, J = 10.7 Hz), 1.62−1.52 (2H, m); ^{13}C NMR ($CDCl_3$) δ 174.9 (C), 174.2 (C), 80.0 (CH), 56.2 (CH), 45.1 (CH), 40.4 (CH_2), 34.8 (CH_2), 31.2 (CH_2), 30.7 (CH_2), 25.7 (CH_2), 22.8 (CH_2); m/e calcd for $C_{11}H_{16}NO_3$ 210.1130, found 210.1130.

(−)-Stemoamide 1. To a solution of desmethylstemoamide **13** (35 mg, 0.167 mmol) in anhydrous THF (1 mL) at − 78 °C was added 1 M LiHMDS solution in THF (0.3 mL). After 1 h, MeI (0.02 mL, 0.32 mmol) was added and stirring was continued for an additional 1 h. The reaction mixture was quenched with saturated ammonium chloride, extracted with ethyl acetate, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel chromatography by eluting with dichloromethane/methanol (9.5:0.5) to give stemoamide (25 mg, 70%): $[\alpha]_D^{25}$ = −187 (c 0.5, CH_3OH); mp = 185−186 °C; ^{1}H NMR ($CDCl_3$) δ 4.21 (1H, dt, J = 10.6, 3.0 Hz), 4.16 (1H, m), 4.00 (1H, dt, J = 10.8, 6.4 Hz), 2.66 (1H, dd, J = 14.3, 12.3 Hz), 2.60 (1H, dq, J = 12.5, 6.8 Hz), 2.45−2.38 (4H, m), 2.09−1.84 (1H, m), 1.90−1.84 (1H, m), 1.72 (1H, quint, J = 10.8 Hz), 1.58−1.49 (2H, m), 1.31 (3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 177.55 (C), 174.22 (C), 77.81 (CH), 56.01 (CH), 52.87 (CH), 40.41 (CH_2), 37.51 (CH), 34.99 (CH_2), 30.81 (CH_2), 25.80 (CH_2), 22.77 (CH_2), 14.30 (CH_3).

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Supporting Information Available: Copies of ^{1}H- and ^{13}C-spectra for selected compounds (**7**, **9**−**11**, and **1**) and ortep drawing and CIF file for the X-ray structure of (−)-stemoamide (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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