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Synthesis of (−)-9,10-*epi*-Stemoamide

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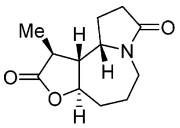
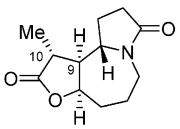
Abstract: An efficient synthesis of (−)-9,10-*epi*-stemoamide has been accomplished in nine steps and 13% overall yield. The synthesis features a lithium hydroxide-promoted fragmentation and an intramolecular 7-*exo-trig* radical cyclization.

Extracts from the roots of *Stemona tuberosa* Lour. and related *Stemona* species have been used in traditional Chinese medicine as anticough agents and insecticides. In 1992, Xu and his colleagues isolated and elucidated the structures of several *Stemona* alkaloids.[1] (−)-Stemoamide (**1**), one of these *Stemona* alkaloids, is composed of a perhydropyrroloazepine ring fused to a γ-butyrolactone moiety, and it contains four contiguous stereogenic centers. Due to its interesting biological activity and structural complexity, it has been a challenging target for synthetic organic chemists. To date, there have been five total syntheses of stemoamides reported in the literature. In 1994, Williams et al. reported the first total synthesis of (−)-stemoamide by a linear approach starting from (*R*)-methyl 3-hydroxy-2-methylpropionate.[2a] The syntheses of both (±)- and (−)-stemoamides by Mori et al. featured a ruthenium-catalyzed enyne metathesis as a key step.[2b,c] Narasaka et al. utilized an oxidative coupling reaction of α-stannyl pyrrolidinone with silyl enol ether.[2d] The total syntheses by Jacobi et al. of both (±)- and (−)-stemoamides used alkyne oxazole Diels−Alder and retro-Diels−Alder reaction sequences to establish the tricyclic skeleton of stemoamide.[2e,f] Recently, Gurjar et al. reported a formal synthesis utilizing a ring-closing metathesis.[2g] Herein, we report an efficient synthesis of (−)-9,10-*epi*-stemoamide (**2**) via a sequential asymmetric Birch reduction−alkylation, lithium hydroxide-promoted fragmentation, and a 7-*exo-trig* radical reaction.



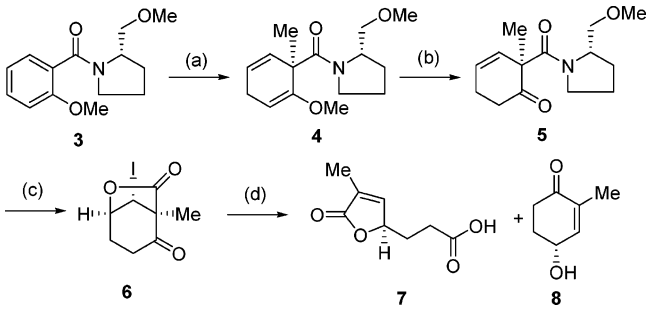
(-)-Stemoamide (1)



(-)-9,10-*epi*-Stemoamide (2)

The synthesis commenced with the preparation of the intermediate **7**, as shown in Scheme 1. Following the procedure developed in our laboratory, Birch reduction of **3** under the standard reaction conditions (K, NH_3, THF, *t*-BuOH, −78 °C) provided the chiral enolate, which was then alkylated in situ with methyl iodide to yield the corresponding 1,4-cyclohexadiene **4** as a single diastereomer.[3] Enol ether hydrolysis of **4** with 6 N aqueous HCl solution in MeOH at room temperature gave the β,γ-enone **5**. Subsequent iodolactonization of **5** with I_2 in THF/H_2O (1:1) at room temperature afforded the enantiomerically pure carbolactone **6** in 81% isolated yield for three steps. Treatment of **6** with lithium hydroxide monohydrate in THF/H_2O (10:1) at room temperature provided the requisite intermediate, butenolide carboxylic acid **7** in 41% yield, along with the side product, 2-methyl-4-hydroxy-2-cyclohexen-1-one (**8**) in 40% yield.[4−6]

SCHEME 1[a]



[a] Reagents and conditions: (a) K, NH_3, THF, *t*-BuOH (1 equiv), −78 °C, piperylene, MeI; (b) 6 N HCl, MeOH, rt; (c) I_2, THF/H_2O (1:1), rt, 81% for three steps; (d) LiOH·H_2O, THF/H_2O (10:1), rt, 41% for **7** and 40% for **8**.

Next, the butenolide carboxylic acid **7** was converted into the phenylthiolactam **12** for radical cyclization, as depicted in Scheme 2. First, **7** was reduced uneventfully to provide the corresponding alcohol **9** in 92% yield by using a borane−tetrahydrofuran complex (BH_3·THF) in THF at −30 °C.[7] Mitsunobu reaction[8](Ph_3P, DEAD, THF, 25 °C) of **9** with succinimide afforded the cyclic imide **10**

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† Deceased January 20, 2000.

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(5) The enantiomeric excesses (ee %) of **7** and **8** were determined by chiral HPLC to be >99 and >96%, respectively.
(6) Compound **7** could be obtained in a slightly better yield by taking a different route (two-step sequence): Schultz, A. G.; Zhang, X. *Chem. Commun.* **2000**, 399.
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(8) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

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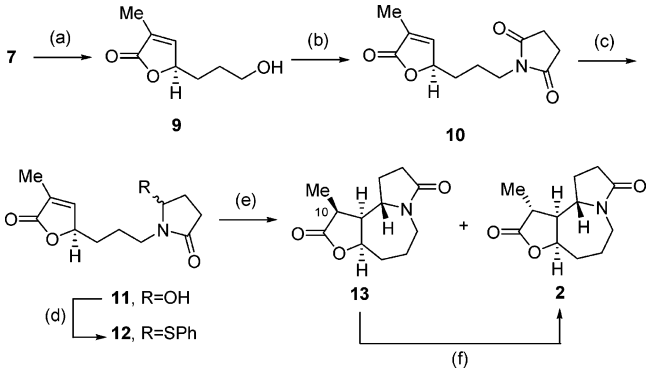
SCHEME 2[a]



[a] Reagents and conditions: (a) BH_3·THF, THF, −30 °C, 92%; (b) succinimide, Ph_3P, DEAD, THF, rt, 92%; (c) $NaBH_4$, MeOH, −10 °C, 88%; (d) PhSH, $TsOH·H_2O$, benzene, 0 °C, 70%; (e) *n*-Bu_3SnH, AIBN, benzene, reflux, 24 h, [c] = 3.5 mM; (f) K_2CO_3, MeOH, rt, 74% for two steps.

in 92% yield. Reduction of cyclic imide was effected with $NaBH_4$ in MeOH at −10 °C to provide the carbinol lactam **11** in 88% yield.[9] Direct treatment of **11** with benzenethiol and *p*-toluenesulfonic acid monohydrate in benzene at 0 °C afforded the required radical reaction substrate, phenylthiolactam **12** in 70% yield.[10]

With phenylthiolactam **12** in hand, we executed the key step, a radical-promoted cyclization.[11] Thus, employing the standard radical reaction protocol, a solution of tributyltin hydride and 2,2′-azobisisobutyronitrile (AIBN) in benzene was added in a period of 24 h to the gently refluxing solution of phenylthiolactam **12** in benzene (final concentration ∼ 3.5 mM). To our delight, the desired intramolecular 7-*exo-trig* radical reaction[12] took place in a remarkably efficient manner, resulting in the formation of a mixture of two diastereomers of constitutional stemoamide (**2** and **13**) as an inseparable mixture (∼10:1).[13] As expected, compounds **2** and **13** are epimers at C-10 with a cis ring fusion stereorelationship at C-8 and C-9 and resulted from the complete facial selective addition (*β*-face addition) of an amido radical to a conjugated C−C double bond of the *γ*-lactone moiety. Subjection of these two diastereomers to K_2CO_3 in MeOH at room temperature furnished only a single stereoisomer **2** in 74% isolated yield. The facile epimerization at C-10 of **13** to **2** is in good accord with the fact that α-Me isomer **2** is thermodynamically more stable than *β*-Me isomer **13** by 2.8 kcal/mol (MM2 calculations).[14]

In summary, we have demonstrated an efficient synthesis of (−)-9,10-*epi*-stemoamide **2**. Lithium hydroxide-promoted fragmentation of carbolactone to butenolide carboxylic acid (**6** → **7**) and the intramolecular 7-*exo-trig* radical cyclization reaction of phenylthiolactam to (−)-9,10-*epi*-stemoamide (**12** → **2**) are noteworthy.

Experimental Section[15]

(5*R*)-5-(3′-Hydroxypropyl)-3-methyl-2(5*H*)-furanone (9). To a solution of butenolide acid **7** (250 mg, 1.5 mmol) in THF (20 mL) was added dropwise BH_3·THF (1.0 M in THF, 1.6 mL, 1.6 mmol) at 0 °C. The resulting solution was stirred overnight at room temperature. The reaction mixture was treated with H_2O and extracted with CH_2Cl_2. The organic layers were isolated, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography (hexanes/EtOAc, 1:1) of the crude residue gave **9** (210 mg, 92%) as a colorless oil: $[\alpha]^{23}_D$ −37.0 (*c* 1.27, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.04−7.03 (m, 1H), 4.91−4.88 (m, 1H), 3.62−3.58 (m, 2H), 2.76 (br s, 1H), 1.84 (d, *J* = 1.9 Hz, 3H), 1.98−1.79 (m, 1H), 1.67−1.57 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 174.5 (s), 149.0 (d), 129.6 (s), 80.9 (d), 61.6 (t), 29.7 (t), 27.8 (t), 10.4 (q); IR *ν* 3422, 2930, 1743 cm^{-1}; CIMS 157 (M^+ + 1, 100); HRMS calcd for $C_8H_{13}O_3$ (M^+ + 1) 157.0870, found 157.0865.

Cyclic Imide (10). To a solution of alcohol **9** (270 mg, 1.7 mmol), triphenylphosphine (500 mg, 1.9 mmol), and succinimide (171 mg, 1.7 mmol) in THF (5 mL) was added diethyl azodicarboxylate (DEAD, 300 *μ*L, 1.9 mmol). The resulting solution was stirred overnight and then concentrated in vacuo. Diethyl ether was added to the residue, and after removal of a white precipitate, the solution was concentrated in vacuo. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 1:2) to give the cyclic imide **10** (377 mg contaminated with a small amount of triphenylphosphine oxide, 92%) as a colorless oil: $[\alpha]^{27}_D$ −29.7 (*c* 0.74, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 6.96 (quint, *J* = 1.5 Hz, 1H), 4.84 (m, 1H), 3.50−3.44 (m, 2H), 2.65 (s, 4H), 1.83 (d, *J* = 1.5 Hz, 3H), 1.74−1.59 (m, 3H), 1.54−1.48 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 177.2, 173.9, 148.1, 130.3, 80.2, 38.1, 30.6, 28.1, 23.4, 10.5; IR (neat) *ν* 2944, 1752, 1700 cm^{-1}; CIMS 238 (M^+ + 1, 100); HRMS calcd for $C_{12}H_{16}NO_4$ (M^+ + 1) 238.1079, found 238.1080.

Carbinol Lactam (11). To a solution of cyclic imide **10** (408 mg, 1.7 mmol) in MeOH (5 mL) was added portionwise $NaBH_4$ (650 mg, 17 mmol) at −10 °C. The resulting solution was stirred for 0.5 h at the same temperature and quenched with water (10 mL). The reaction mixture was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the residue (388 mg, 94%). Flash column chromatography (EtOAc) of the residue gave the carbinol lactam **11** (362 mg, 88%) as a colorless oil: $[\alpha]^{25}_D$ −29.4 (*c* 0.34, $CHCl_3$); ^{1}H NMR (diastereomeric mixture, 500 MHz, $CDCl_3$) *δ* 7.04 (q, *J* = 1.5 Hz) and 7.03 (q, *J* = 1.5 Hz, 1H), 5.23−5.02 (m, 1H), 4.96−4.91 (m, 1H), 3.67−3.04 (m, 2H), 2.58−2.50 (m, 1H), 2.37−2.22 (m, 3H), 1.85 (d, *J* = 1.7 Hz) and 1.85 (d, *J* = 1.9 Hz, 3H), 2.02−1.45 (m, 5H); ^{13}C NMR (diastereomeric mixture, 126 MHz, $CDCl_3$) *δ* 175.1, 175.0, 174.5 (overlapped), 149.0, 148.9, 129.9, 129.8, 83.4, 83.1, 80.9, 80.7, 39.7, 39.3, 30.6, 30.5, 28.9, 23.4, 23.3, 10.5; IR (neat) *ν* 3403, 2930, 1752, 1670 cm^{-1}; CIMS 222 (M^+ − 18, 100); HRMS calcd for $C_{12}H_{18}NO_4$ (M^+ + 1) 240.1235, found 240.1226.

Phenylthiolactam (12). To a solution of carbinol lactam **11** (117 mg, 0.50 mmol) in benzene (3 mL) was added *p*-TsOH (1 mg) and thiophenol (75 *μ*L, 0.73 mmol) at 0 °C. The resulting solution was stirred at room temperature overnight, diluted with diethyl ether, and washed with water. The organic layers were

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(13) The ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.

(14) ^{1}H and ^{13}C NMR spectra of **2** were identical to those prepared by Jacobi and Lee (see ref 2e).

(15) For general experimental procedures and full characterization data of **3**−**8**, see ref 4b.

isolated, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 1:3) to give the phenylthiolactam **12** (112 mg, 70%) as a colorless oil: $[\alpha]^{25}_D$ −10.2 (*c* 0.59, $CHCl_3$); ^{1}H NMR (diastereomeric mixture, 500 MHz, $CDCl_3$) δ 7.41−7.39 (m, 2H), 7.35−7.30 (m, 3H), 7.00 (br t, J = 1.5 Hz, 1H), 6.98 (br t, J = 1.5 Hz, 1H), 4.92−4.87 (m, 2H), 3.80−3.69 (m, 1H), 3.35−3.27 (m, 1H), 2.49−2.40 (m, 1H), 2.22−2.17 (m, 1H), 2.12−2.05 (m, 1H), 1.90 (br t, J = 1.5 Hz, 3H), 1.89 (br t, J = 1.5 Hz, 3H), 1.81−1.62 (m, 3H), 1.60−1.46 (m, 2H); ^{13}C NMR (diastereomeric mixture, 126 MHz, $CDCl_3$) δ 174.7, 174.6, 174.1, 174.0, 148.5, 148.3, 135.0, 134.9, 132.1, 130.6, 130.5, 130.2, 130.1, 129.3, 129.0, 128.9, 80.3, 80.2, 67.1, 67.0, 39.7, 39.4, 30.7, 30.6, 29.1, 29.0, 26.6, 26.5, 22.7, 22.5, 10.6, 10.5; IR (neat) ν 1752, 1686 cm^{-1}; CIMS 332 (M^+ + 1, 3), 222 (100); HRMS calcd for $C_{18}H_{22}NO_3S$ (M^+ + 1) 332.1320, found 332.1315.

(−)-9,10-*epi*-Stemoamide (2). To a solution of phenylthiolactam **12** (74 mg, 22 μmol, 5.5 mM) in benzene (40 mL) was added a solution of *n*-Bu_3SnH (93 μL, 33 mmol) and AIBN (11 mg, 6.7 μmol) in benzene (25 mL) via a syringe pump over a period of 24 h at 85 °C (oil bath temperature). The resulting solution was stirred at reflux for an additional 24 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in diethyl ether, and DBU[16] was added until the white precipitate remained. Then, iodine was added until the yellow color remained. The resulting suspension was passed through a short column to remove tin material. The solution was concentrated in vacuo, dissolved in MeOH (2 mL), and treated with K_2CO_3 (30 mg, 22 μmol). The resulting reaction mixture was stirred at room temperature for 48 h and concentrated. The residue was then treated with water, neutralized with 10% aqueous HCl solution, and extracted with CH_2Cl_2. The organic layers were isolated, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 1:10) to give **2** (37 mg, 74%) as the only detectable product, a colorless semisolid: $[\alpha]^{21}_D$ −63.3 (*c* 1.69, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (ddd, J = 10.6, 7.8, 2.7 Hz, 1H), 4.17 (dt, J = 13.8, 4.7 Hz, 1H), 3.61 (dd, J = 9.8, 7.8 Hz, 1H), 2.76 (ddd, J = 13.9, 10.6, 3.4 Hz, 1H), 2.58−2.53 (m, 1H), 2.48 (m, 1H), 2.41 (m, 1H), 2.35−2.24 (m, 2H), 2.11−2.06 (m, 1H), 1.95−1.80 (m, 3H), 1.65−1.57 (m, 1H), 1.37 (d, J = 7.1 Hz, 3H); ^{1}H NMR (500 MHz, C_6D_6) δ 3.98 (dtd, J = 13.6, 4.6, 0.8 Hz, 1H, H-5a), 3.80 (ddd, J = 11.0, 8.1, 3.0 Hz, 1H, H-8), 2.42 (ddd, J = 9.9, 8.1, 1.6 Hz, 1H, H-9a), 2.07 (ddd, J = 13.7, 10.5, 3.4 Hz, 1H, H-5b), 1.95 (ddd, J = 16.6, 8.5, 10.9 Hz, 1H, H-2), 1.82 (ddd, J = 16.6, 9.5, 1.1 Hz, 1H, H-2), 1.65 (dq, J = 8.6, 7.4 Hz, 1H, H-10), 1.48−1.44 (m, 1H, H-7), 1.37 (dt, J = 10.1, 8.3 Hz, 1H, H-9), 1.28−1.20 (m, 1H, H-1b), 1.19−1.08 (m, 2H, H-6a and H-7), 1.00−0.92 (m, 1H, H-6a), 0.84 (d, J = 7.4 Hz, 3H, H-12), 0.85−0.80 (m, 1H, H-1a); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 174.6, 80.7, 60.5, 50.7, 44.0, 39.0, 30.0, 28.9, 25.4, 23.9, 15.8; ^{13}C NMR (126 MHz, C_6D_6) δ 177.4 (s), 173.6 (s), 80.4 (d), 60.0 (d), 50.6 (d), 43.9 (t), 38.9 (d), 30.3 (t), 29.1 (t), 25.5 (t), 24.6 (t), 15.9 (q); IR (neat) ν 2938, 1769, 1686 cm^{-1}; CIMS 224 (M^+ + 1, 100); HRMS calcd for $C_{12}H_{18}NO_3$ (M^+ + 1) 224.1286, found 224.1289.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of new compounds **2** and **9**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049083I

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