Synthesis of (+)-9a-*epi*-Stemoamide via DBU-Catalyzed Michael Addition of Nitroalkane

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Abstract: We describe a practical synthesis of (+)-9a-*epi*-stemoamide, which has been achieved in six steps from α,β-unsaturated γ-butyrolactone. The main features of the current approach include a DBU-catalyzed Michael addition of nitroalkane and a reductive lactamization of nitro esters.

Key words: Michael addition, nitroalkane, stemoamide, synthesis, unsaturated butyrolactone

The extracts from Stemona species have been reportedly applied against insect pests. Moreover, practitioners of traditional Chinese and Japanese medicine have utilized the roots of *Stemona tuberosa* Lour. and related Stemona species to treat respiratory diseases such as asthma, bronchitis, petusis, and tuberculosis.[3] Extensive phytochemical investigations have led to the isolation of more than 70 alkaloids of the Stemonacea family, many of which possess an aza-azulene framework.[4] (–)-Stemoamide (**1**, Figure 1), the structurally simplest member of the family, was isolated along with another five structurally related alkaloids from *Stemona tuberosa* by Xu and co-workers in 1992. The structure of **1** can be conceived as a butyrolactone fused to a pyrrolo[1,2a]-azepine nucleus and four contiguous stereocenters are imbedded in the tricyclic skeleton.[5] Due to its potential bioactivities and unique structural features, stemoamide (in both racemic[6,7] and enatiomerically pure[7b,8–12,13b,14] form) has emerged as an attractive target for total synthesis. The first total synthesis of natural **1** was described by Williams[8] in 1994. Remarkably, Jacobi[7] accomplished a seven-step total synthesis of **1** in both racemic and *levo*-form featuring a Diels–Alder/retro-Diels–Alder reaction sequence. In order to exploit the full utilities of stemoamide in drug development, synthesis of stemoamide analogues recently began to gain increasing attention, as demonstrated by the work coming out of the Schultz[15] and Cossy[13a,c] groups.

As a part of our continuing endeavors in investigating medicinally useful natural alkaloids and derivatives, we have been interested in developing a practical and scalable method for constructing (+)-9a-*epi*-stemoamide (**2**, Figure 1), an analogue of (–)-stemoamide (**1**). The retrosynthetic analysis (Scheme 1) reveals that **1** and/or **2** may be derived from **3** by alkylative cyclization and chemo- and stereoselective enolate methylation. Bicycles **3** should be accessible through reductive lactamization of nitro esters **4**, which in turn can be obtained from α,β-unsaturated-butyrolactone **5** via DBU-catalyzed Michael addition.

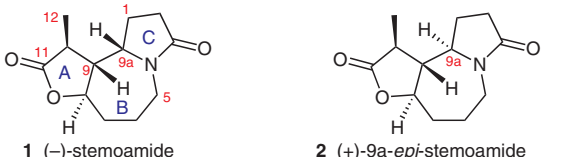
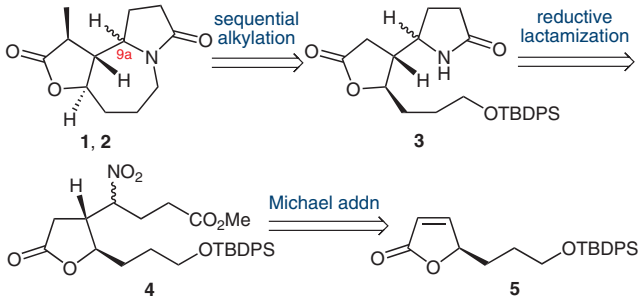


Figure 1 (–)-Stemoamide (**1**) and (+)-9a-*epi*-stemoamide (**2**)



Scheme 1 Strategy for constructing the tricyclic skeleton of stemoamide

As outlined in Scheme 2, the present synthesis commenced from methyl 4-nitrobutanoate,[16] which, after being catalytically deprotonated at the nitro-bearing carbon in the presence of DBU[17] (10 mol%), attacked α,β-unsaturated-butyrolactone **5**[18] at the β-position and stereoselectively from the face opposite to the silyloxypropyl group. Both adducts from the Michael addition seemed to have an *R*-configuration at C-9 (corresponding to the numbering system for stemoamide) although only moderate stereocontrol was observed at C-9a (dr = 2:1). The two inseparable epimers **4**, furnished in 89% combined yield, were suitable for use directly in the subsequent transformations. Treatment with Raney Ni under an atmosphere of H_2 gas led to direct conversion of nitro esters **4** to lac-

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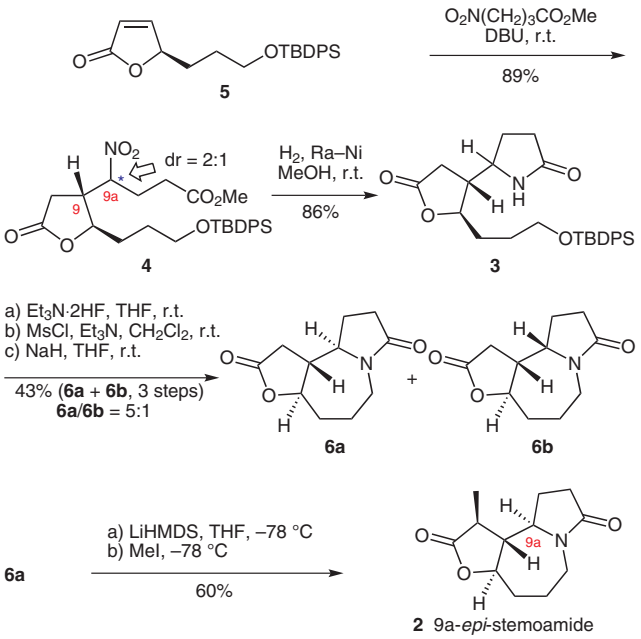
tams **3** (86%) through hydrogenation of the nitro group followed by lactamization. Desilylation of **3** and hydroxyl sulfonation generated a pair of diastereomeric mesylates, which were subjected[19] to an excess amount of NaH to afford tricycles **6a** and **6b** in a combined yield of 43% (over the three steps from **3**). Notably, epimers **6a** and **6b** were produced in a 5:1 ratio because the cyclization of the two mesylates (mixture, dr = 2:1) took place via intramolecular S_N2 displacement at considerably different rates under the reaction conditions, coinciding in what was observed by Cossy and co-workers.[13c] Compounds **6a** (a solid) and **6b** (an oil[14]) were inseparable by silica gel column chromatography. Fortunately, careful recrystallization of the mixture from EtOAc–MeOH (100:1) resulted in reaping **6a** in pure form. Finally, deprotonation of **6a** with LiHMDS followed by trapping with MeI provided the target molecule **2** in 60% yield. For the first time, (+)-9a-*epi*-stemoamide (**2**) was synthesized as a single pure compound, even though the synthesis of a mixture of **1** and **2** (both in racemic form) has been disclosed in the literature[13c] previously.



Scheme 2 Synthesis of (+)-9a-*epi*-stemoamide (**2**)

In summary, we have realized a practical six-step[20] assembly of (+)-9a-*epi*-stemoamide (**2**) from α,β-unsaturated butyrolactone **5**. The main features of the current approach include DBU-catalyzed Michael addition of nitroalkane and reductive lactamization of nitro esters **4**.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

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(18) For the preparation of *ent*-(+)-**5** {Lit.[18a] $[\alpha]_D^{25}$ +31.5 (*c* 2.00)}, see: (a) Hanessian, S.; Hodges, P. J.; Murray, P. J.; Sahoo, S. P. *J. Chem. Soc., Chem. Commun.* **1986**, 754. The enantiomer, **5** {$[\alpha]_D^{25}$ –32.7 (*c* 2.4, $CHCl_3$)}, was synthesized in a similar manner[18a] from (*R*)-*tert*-butyl[3-(oxiran-2-yl)propoxy]diphenylsilane, an epoxide prepared[18b–d] from L-ascorbic acid: (b) Hubschwerlen, C. *Synthesis* **1986**, 962. (c) Sharma, G. V. M.; Punna, S.; Krishna, P. R.; Chorghade, M. S.; Ley, S. V. *Tetrahedron: Asymmetry* **2005**, *16*, 1125. (d) Brimble, M. A.; Park, J. H.; Taylor, C. M. *Tetrahedron* **2003**, *59*, 5861.
(19) This was performed by following Narasaka's protocol.[6]
(20) **Preparation of New Compounds**
Compounds 4: Compound **5** (1.00 g, 2.63 mmol) was mixed with methyl 4-nitrobutanoate (580 mg, 3.94 mmol), and DBU (40 mg, 0.26 mmol) was introduced into the system. The mixture was stirred with no solvent at r.t. for 24 h and concentrated. The residue was chromatographed (PE–EtOAc, 5:1) to afford **4** (1.23 g, 89%) as a colorless oil (2:1 epimers).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 9 H), 1.05–1.92 (m, 4 H), 2.01–2.58 (m, 5 H), 2.62–2.84 (m, 2 H), 3.69 (s, 3 H), 3.60–3.79 (m, 2 H), 4.32–4.42 (m, 1 H), 4.58–4.72 (m, 1 H), 7.38–7.42 (m, 6 H), 7.63–7.68 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 26.3, 26.8, 28.1, 29.3, 29.4, 30.9, 31.0, 31.6, 31.9, 43.4, 43.5, 52.0, 62.7, 62.8, 80.6, 82.0, 87.7, 88.3, 127.6, 127.6, 129.6, 129.6, 133.5, 133.6, 135.5, 171.9, 172.0, 173.7, 173.8. ESI-MS: *m/z* (%) = 550 (100) [M + 1], 450 (7). Anal. Calcd for $C_{28}H_{37}NO_7Si$: C, 63.73; H, 7.07; N, 2.65. Found: C, 64.02; H, 7.10; N, 2.62.

Compounds 3: Freshly prepared Raney Ni (ca. 1.20 g) was added to a solution of compound **4** (1.91 g, 3.62 mmol) in MeOH (72 mL). The mixture was hydrogenated under one atmosphere of hydrogen at r.t. for 24 h. After Raney Ni was filtered off, the filtrate was concentrated to give a residue, which was chromatographed (CH_2Cl_2–MeOH, 30:1) to afford compound **3** (1.455 g, 86%) as a colorless oil (2:1 epimers). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 9 H), 1.60–1.74 (m, 5 H), 2.26–2.40 (m, 5 H), 2.62–2.72 (m, 1 H), 3.64–3.75 (m, 3 H), 4.25–4.38 (m, 1 H), 7.34–7.43 (m, 6 H), 7.60–7.66 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 24.5, 25.2, 26.8, 28.2, 29.8, 30.0, 30.6, 30.7, 31.6, 32.3, 45.3, 45.6, 55.5, 56.2, 63.0, 63.2, 81.9, 82.5, 127.7, 129.7, 133.6, 135.5, 175.3, 178.8, 179.0. ESI-MS: *m/z* (%) = 520 (13) [M + Na + MeOH], 504 (8) [M + K], 488 (97) [M + Na]. ESI-HRMS: *m/z* calcd for $C_{27}H_{35}NO_4SiNa$ [M + Na]: 488.2233; found: 488.2228. Anal. Calcd for $C_{27}H_{35}NO_4Si$: C, 69.64; H, 7.58; N, 3.01. Found: C, 69.20; H, 7.43; N, 2.89.

Compound 6a: To a stirred solution of compounds **3** (1.30 g, 2.79 mmol) in THF (20 mL), $Et_3N{\cdot}2HF$ (2.00 mL, 13.9 mmol) was added, and the mixture was stirred at r.t. for 3 d. $NaHCO_3$ (1.20 g, 14.3 mmol) was added, and the mixture was stirred for 10 min. The solvent was concentrated to give a residue, which was chromatographed (EtOAc–MeOH, 10:1) to afford the epimeric primary alcohols (842 mg) as a pale yellow solid. The alcohols were dissolved in CH_2Cl_2 (10 mL), and then DMAP (34 mg, 0.28 mmol), Et_3N (1.20 mL, 8.61 mmol), and MsCl (0.32 mL, 4.18 mmol) were added sequentially. The mixture was stirred at r.t. overnight, neutralized with sat. aq $NaHCO_3$ solution, extracted with $CHCl_3$–*i*-PrOH (4:1; 3 × 40 mL), dried (Na_2SO_4), and filtered. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (EtOAc–MeOH, 4:1) to give the mesylation products. The mesylates were dissolved in THF (50 mL) and added to a stirred suspension of NaH (60%, 1.12 g, 28.0 mmol) in THF (150 mL) at 0 °C. After warming to r.t. and stirring for 20 h, the reaction was quenched at 0 °C by the addition of sat. aq NH_4Cl solution. The mixture was extracted with $CHCl_3$–*i*-PrOH (4:1), and the combined organic layers were dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (EtOAc–MeOH, 100:1) to afford a mixture of **6a** and **6b** (252 mg, 43% over the three steps from **3**) as a white solid. The ratio of **6a**/**6b** was found to be ca. 5:1 according to the line integrals of the ^{1}H NMR spectrum. A pure sample of **6a** was obtained by careful recrystallization of the 5:1 mixture of **6a**/**6b** from EtOAc–MeOH (100:1).

Analytical Data of Compound 6a: Mp 106–108 °C; $[\alpha]_D^{28}$ +23.3 (*c* 0.52, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58–1.90 (m, 4 H), 2.14–2.53 (m, 6 H), 2.60–2.68 (m, 1 H), 3.13–3.22 (m, 1 H), 3.54 (dd, *J* = 16.5, 7.5 Hz, 1 H), 3.78–3.87 (m, 1 H), 4.31–4.41 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 24.1, 30.1, 30.4, 32.9, 40.3, 48.5, 60.8, 83.2, 174.0, 174.5. MS (EI): *m/z* (%) = 209 (31) [M^+], 191 (7), 124 (19), 110 (33), 98 (100). HRMS (EI): *m/z* calcd for $C_{11}H_{15}NO_3$ [M^+]: 209.1052; found: 209.1047.

Compound 2: To a solution of **6a** (22 mg, 0.11 mmol) in anhyd THF (1 mL) at –78 °C was added LiHMDS solution in THF (1.0 M, 0.19 mL, 0.19 mmol). After 1 h, MeI (13 μL, 0.21 mmol) was added at –78 °C, and the stirring was continued for an additional 1 h. The reaction mixture was quenched with sat. NH_4Cl, warmed to r.t., and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a residue, which was purified by silica gel chromatography (EtOAc–MeOH, 15:1) to furnish **2** (14 mg, 60%) as a white solid: mp 86–88 °C; $[\alpha]_D^{28}$ +74.9 (*c* 0.30, MeOH). ^{1}H NMR (300 MHz $CDCl_3$): δ = 1.29 (d, *J* = 7.5 Hz, 3 H), 1.62–1.90 (m, 4 H), 2.18–2.56 (m, 5 H), 2.75–2.88 (m, 1 H), 2.98–3.09 (m, 1 H), 3.60–3.69 (m, 1 H), 3.83–3.93 (m, 1 H), 4.52 (dt, *J* = 10.5, 4.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.8, 21.6, 23.2, 30.0, 30.2, 38.4, 40.8, 52.3, 57.8, 80.5, 174.0, 178.0. MS (EI): *m/z* (%) = 223 (37) [M^+], 208 (21), 180 (20), 98 (100). HRMS (EI): *m/z* calcd for $C_{12}H_{17}NO_3$ [M^+]: 223.1208; found: 223.1207.