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Free-Radical Approaches to Stemoamide and Analogues

Nicolas Bogliotti, Peter I. Dalko, and Janine Cossy*

Laboratoire de Chimie Organique, associé au CNRS, ESPCI, 10 rue Vauquelin, 75231, Paris Cedex 05, France

janine.cossy@espci.fr

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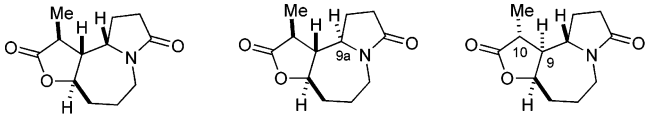

Two approaches allowing access to the tricyclic stemona backbone are presented. Both approaches rely on a free-radical cyclization reaction as the key step. In the formal synthesis of (±)-stemoamide, the construction of the A ring of the natural product was achieved via a 5-*exo-trig* radical cyclization with atom transfer. The two diastereoisomers issuing from this cyclization showed different reactivity while forming the seven-membered ring of the final product. In the second part of this study, a 7-*exo-trig* free radical cyclization was realized allowing access to the (±)-9,10-bis-*epi*-stemoamide. This reaction was highly stereoselective and allowed the control of three of the four contiguous stereocenters present in the molecule.

The roots of *Stemona tuberosa* Lour. and related stemona species have been used in traditional Asian folk medicine in the treatment of respiratory diseases such as asthma, bronchitis, petusis, and tuberculosis,[1] and extracts have been utilized as insecticides and antihelmintics.[2] To date, more than 70 alkaloids of the family of Stemonacea have been isolated, many of them possessing an aza-azulene skeleton.[3] The structurally simplest member, (−)-stemoamide, which was isolated from *Stemona tuberosa*, consists of a γ-butyrolactone fused to a pyrrolo[1,2*a*]-azepine core and possesses four contiguous stereocenters (Figure 1).[4] Although a considerable amount of work has been devoted to the synthesis of both racemic[5] and natural (−)-stemoamide,[6] only little attention has been paid to the preparation of analogues.[7,8] Recently, Schultz et al.[9] and our group[10] have reported two short syntheses of 9,10-bis-*epi*-stemoamide. As

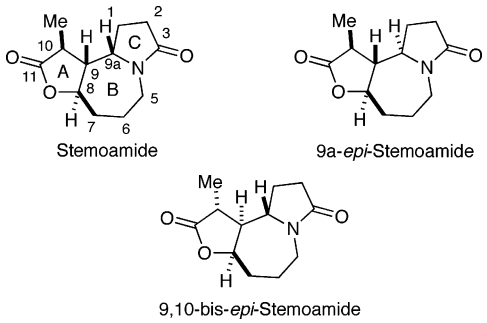

FIGURE 1. Stemoamide, 9a-*epi*-stemoamide and 9,10-bis-*epi*-stemoamide.

part of our continuing interest in the synthesis of *Stemona* derivatives, we wish to report herein a short synthetic study, which provides access to (±)-stemoamide, as well as to (±)-9a-*epi*-stemoamide and to (±)-9,10-bis-*epi*-stemoamide (Figure 1).

Formal Synthesis of (±)-Stemoamide. The key step of the synthesis is the construction of the lactone ring using a free radical 5-*exo-trig* atom transfer cyclization of the halogeno-ester **D**, which would produce compound of type **C** (Scheme 1). Although the relative C8/C9 stereochemistry of the cyclization could be anticipated to be *trans* by analogy with the literature,[11] the control of the C9a stereogenic center was uncertain (Scheme 1).

The synthesis of stemoamide commenced with the preparation of the monoprotected diol **3**, which was synthesized from 2,3-dihydrofuran (**1**), using a modified literature protocol (Scheme 2).[12] The acid-catalyzed hydration of 2,3-dihydrofuran (**1**), followed by the addition of vinylmagnesium bromide to the resulting hemiacetal, afforded a mixture of diol **2** and protected allylic alcohol **3** in 10% and 18% yield, respectively. Despite the poor yield of protected allylic alcohol **3**, the low cost of the starting material and the reproducibility on large scale allowed the preparation of multigram quantities of **3**. Compound **3** was then converted to the unsaturated bromoester **4** by addition of bromoacetyl bromide in the presence of pyridine, and this latter product was subjected to a cross-metathesis (CM) with ethyl 4-pentenoate[13] (1.5 equiv) in the presence of the second generation Grubbs' catalyst **G-II**[14] in refluxing CH_2Cl_2 to afford

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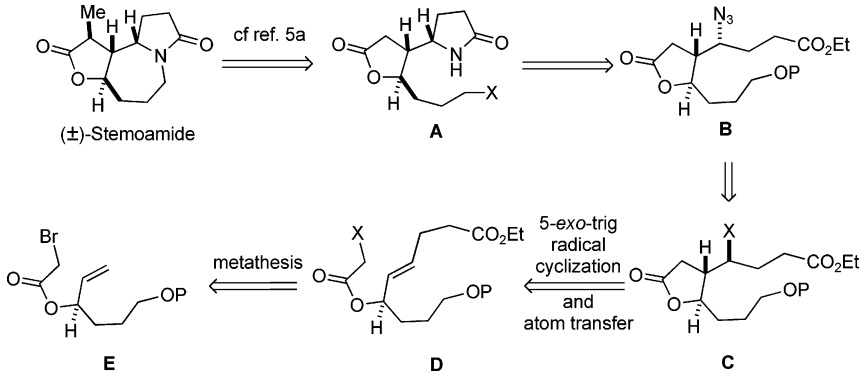
SCHEME 1

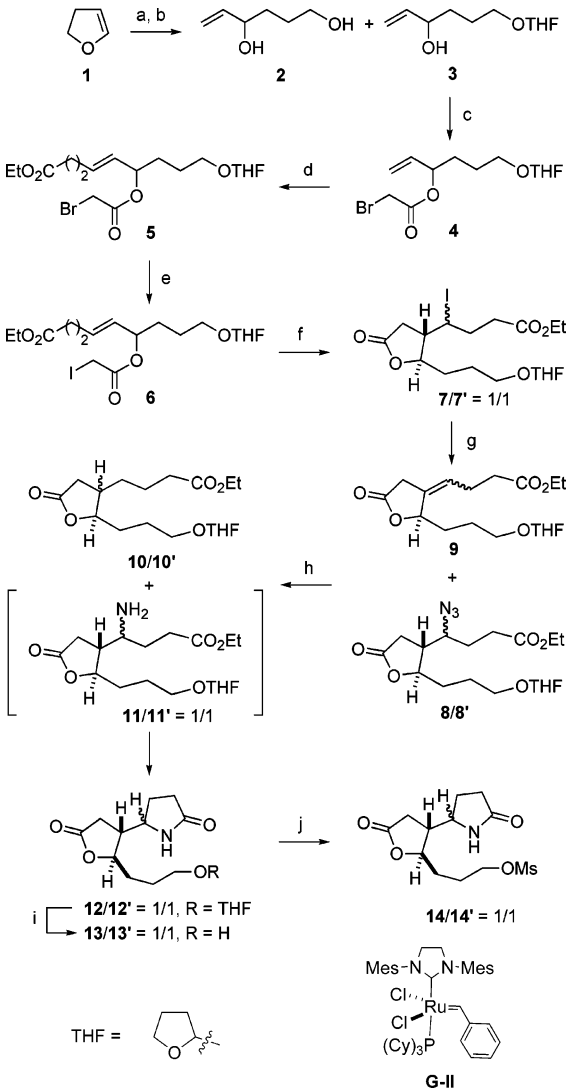


olefin **5** in 54% yield (84% based on recovered **4**). It is worth noting that this sequence proved more viable than the alternative direct cross-metathesis between **3** and ethyl 4-pentenoate, as the corresponding CM product was isolated in low yield (28%) as a result of the competitive isomerization of olefin of **3**.[15] As the bromide **5** was unreactive under our chosen radical cyclization conditions (dilauryl peroxide, refluxing benzene),[11] **5** was transformed to the more reactive iodide **6** by using LiI in DMF (75%). The key radical cyclization was performed in the presence of a catalytic amount of dilauryl peroxide in refluxing benzene to afford a roughly equimolar mixture of inseparable iodolactones **7** and **7′** in 65% yield (81% yield based on recovered **6**). In order to form the lactam ring, **7** and **7′** were treated with NaN_3 in DMF at 80 °C. Under these conditions **8** and **8′** were formed, as well as the unsaturated lactone **9** resulting from the elimination of iodine. As **8**, **8′**, and **9** also proved to be inseparable, the mixture of these three compounds was directly hydrogenated in the presence of Pd/C (10%) catalyst in MeOH, leading to a 1/1 diastereomeric mixture of lactones **10**/**10′** and amines **11**/**11′**. Amines **11**/**11′** cyclized rapidly under the reaction conditions to produce the lactams **12**/**12′** (1/1 mixture) in 44% yield from **7**/**7′**. The tetrahydrofuranyl protecting group of **12**/**12′** was removed in the presence of a catalytic amount of *p*-TSA in MeOH, to afford the alcohols **13**/**13′**, which were treated with methanesulfonyl chloride (Et_3N, CH_2Cl_2) to give the corresponding mesylates **14**/**14′** as a 1:1 mixture in 83% yield.

As the mesylates **14**/**14′** proved to be inseparable, the 1/1 diastereomeric mixture of compounds were cyclized under Narasaka's conditions ($c = 0.01$ M, NaH, THF).[5a] Under these conditions, it was observed that the cyclization of the two diastereoisomers **14** and **14′** occurred at different rates, as the ^{1}H NMR monitoring of the crude mixture indicated the formation of the tricyclic compounds **15** and **15′** in a ratio of 3/1. After purification by flash chromatography on silica gel, the cyclized products **15** and **15′** were obtained with the same 3/1 ratio of isomers in 60% yield (Scheme 3).

The difference in the rate of the cyclization of the two diastereomers **14** and **14′** can be rationalized by examination of the steric interactions resulting from the formation of the

SCHEME 2[a]



[a] Reagents and conditions: (a) HCl 0.2 N; (b) vinylmagnesium bromide, THF (**2**, 10%; **3**, 18%); (c) bromoacetyl bromide, pyridine, CH_2Cl_2 (85%); (d) second generation Grubbs' catalyst **G-II** (2 mol %), ethyl 4-pentenoate (1.5 equiv), CH_2Cl_2, 40 °C (54%, 84% based on recovered **4**); (e) LiI (10 equiv), DMF, rt (75%); (f) DLP (30 mol %), benzene, 80 °C, 45 min (65% yield, 81% yield based on recovered **6**); (g) NaN_3, DMF, 80 °C, 1 h; (h) H_2, Pd/C, MeOH (**10**/**10′**, 26% for 2 steps; **11**/**11′**, 44% for 2 steps); (i) *p*-TSA (cat.), MeOH (93%); (j) methanesulfonyl chloride, Et_3N, CH_2Cl_2 (89%).

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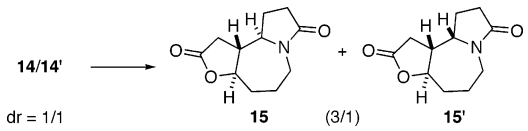
SCHEME 3[a]



[a] Reagents and conditions: NaH, THF, *c* 0.01 M, 60%.

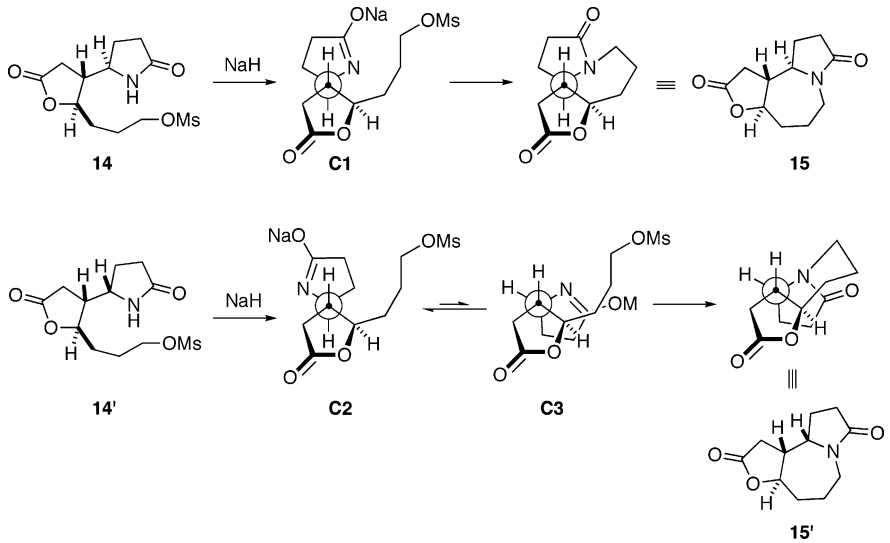
required transition state for the ring closure. In the case of the enolate derived from **14**, the conformation **C1**, which minimizes the steric interactions between the lactone and the pyrrolidinone ring, results in a proximity between the nitrogen atom and the carbon atom bearing the mesylate group. On the contrary, in order to undergo cyclization, the enolate derived from **14′** must react via the unfavorable sterically congested conformation, thus dramatically decreasing the rate of the cyclization for this diastereomer. Noteworthy in this sequence, compound **15** is the precursor of (±)-9a-*epi*-stemoamide and compound **15′** is the precursor of (±)-stemoamide. As the racemic tricyclic intermediate **15′** was previously transformed into (±)-stemoamide in one step,[5a] the presented sequence corresponds to a formal synthesis of (±)-stemoamide.

Synthesis of (±)-9,10-bis-epi-Stemoamide. The construction of the tricyclic stemona backbone was envisaged by a free-radical cyclization of intermediate **F** (Scheme 5). This 7-*exo-trig* cyclization would allow the control of three of the four stereocenters of the final product. The stereochemical outcome of the reaction was difficult to predict at this stage of our studies, except as previously the likely relative *trans* stereochemistry at C9/C9a. As preliminary studies indicated that thioaryl ethers can be a convenient source of pyrrolidinone radicals under tin hydride mediated thermal radical conditions,[16] the α,*β*-unsaturated lactone **22** could be a good radical precursor for obtaining stemoamide and/or analogues (Scheme 5).

The synthesis of the advanced intermediate **22** from compound **2** is depicted in Scheme 6. Diol **2** was doubly protected using standard silylation conditions (TBSCl, imidazole, 93%), and the primary silyl protecting group was then selectively removed by treatment of **16** with NH_4F in refluxing MeOH. The lactam ring of the stemoamide was introduced by using a Mitsunobu-type substitution of the free hydroxyl of **17** by succinimide (DIAD, PPh_3, THF; 91%).[17] The resulting imide **18** was selectively transformed into **19** by reduction with the superhydride $LiEt_3BH$, in THF at −78 °C (87%), and the thiophenyl radical precursor was prepared from compound **19** by treatment with PhSH in the presence of *p*-TSA (87%). It is worth noting that under these acidic conditions, the silyl protecting group was also removed. After esterification of methacrylic acid with the allylic alcohol **20**, in the presence of DCC and DMAP, the obtained ester **21** was transformed into lactone **22** by using a RCM reaction. Among the tested conditions, the best results were obtained with the second generation Grubbs' catalyst **G-II**, and lactone **22** was isolated in 79% yield. With the radical precursor in hand, the 7-*exo-trig* cyclization was performed. Treatment of **22** with Bu_3SnH and AIBN (cat.) in refluxing benzene (c = 5 mM) led to the tricyclic (±)-9,10-bis-*epi*-stemoamide as a single diastereoisomer in a nonoptimized 20% yield. It is worth noting that although the ^1H NMR and GC/MS analysis of the crude reaction mixture showed the presence of two diastereoisomers in a ratio of 2.5/1, only one compound could be isolated after flash column chromatography on silica gel. The relative configuration of the three newly formed contiguous centers was assigned by comparison of the ^1H and ^{13}C NMR data with those previously reported by Jacobi and Lee.[5b] In addition, this result was further confirmed by Khim and Schultz, who reported a similar free-radical approach for the construction of the seven-membered ring of (−)-9,10-bis-*epi*-stemoamide.[9]

Free-radical approaches to (±)-stemoamide as well as to stemoamide derivatives have been presented. The formal synthesis of (±)-stemoamide has been realized by using a 5-*exo-trig* radical cyclization with atom transfer, and this key cyclization allowed the control of two of the four contiguous stereocenters of the final product. The two diastereoisomers resulting from this radical cyclization showed different reactivity in the formation of the seven-membered ring of the final product as the precursor of (±)-stemoamide cyclized much slower than its epimer, a precursor of (±)−9a-*epi*-stemoamide. In the second part of this study a 7-*exo-trig* free radical cyclization was performed, leading to the synthesis of (±)-9,10-bis-*epi*-stemoamide with the control of three of the four contiguous stereocenters present in the molecule.

SCHEME 4



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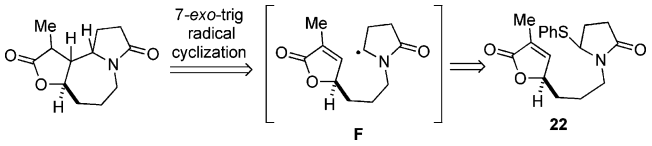
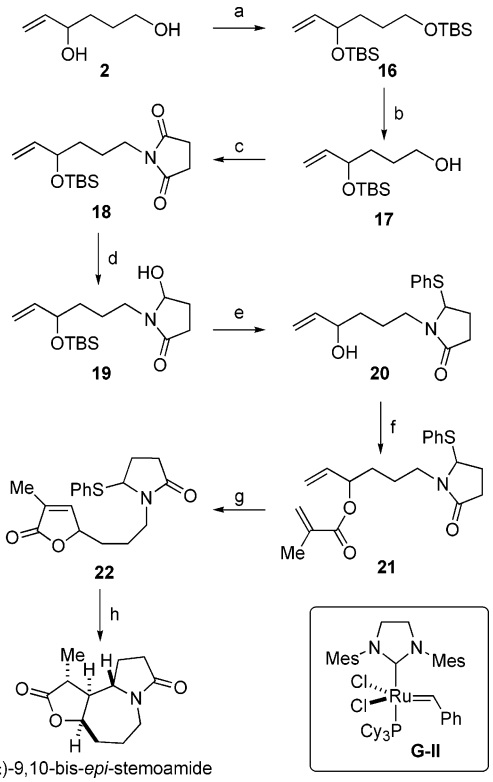


SCHEME 6[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2 (93%); (b) NH_4F, MeOH, 65 °C (58%); (c) succinimide, DIAD, PPh_3, THF (91%); (d) $LiBEt_3H$, THF, −78 °C (96%); (e) *p*-TSA (cat.), PhSH (87%); (f) methacrylic acid, DCC, DMAP (cat.), CH_2Cl_2 (86%); (g) **G-II** (10 mol %), CH_2Cl_2, 40 °C, 3 h (79%); (h) Bu_3SnH, AIBN, benzene (*c* 5 mM), 80 °C (20%).

Experimental Section

Ethyl 4-Iodo-4-{(2*R,3*S**)-5-oxo-2-[3-(tetrahydrofuran-2-yloxy)-propyl]-tetrahydrofuran-3-yl}-butyrate (7 and 7′).** A solution of **6** (3.21 g, 7.1 mmol) and dilauroyl peroxide (845 mg, 2.12 mmol, 0.3 equiv) in benzene (35 mL) was degassed by bubbling argon through the solution for 10 min. After refluxing for 45 min, the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (gradient petroleum ether/EtOAc 4/1, 1/1) to afford a mixture of **7** and **7′** (**7**/**7′** = 1/1, 2.08 g, 4.6 mmol, 65% yield, 81% yield based on recovered **6**) as a colorless oil. $C_{17}H_{27}IO_6$. MW: 454.30. R_f: 0.54 (petroleum ether/EtOAc 1/1). IR (film): 2933, 1772, 1728, 1179, 1034 cm^{-1}. ^1H NMR (400 MHz): δ 5.03 (dd, J = 3.8, 1.1 Hz, 1H), 4.41 (m, 0.5H), 4.34 (m, 0.5H), 4.19 (m, 0.5H), 4.08 (m, 2.5H), 3.83−3.77 (m, 2H), 3.68−3.58 (m, 1H), 3.38−3.33 (m, 1H), 2.71 (m, 1H), 2.58−2.31 (m, 4H), 1.98−1.55 (m, 10H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz): δ 174.7, 172.0−171.9, 103.8, 84.9−84.3, 66.8, 66.2, 60.7, 47.5−47.2, 39.4−38.6, 34.3, 33.8−33.7, 32.8−32.7, 32.2, 31.9−31.8, 25.6−25.4, 23.4, 14.1. MS (EI) *m*/*z* (relative intensity): 367 (4), 239 (13), 211 (19), 71 (100), 70 (12). Anal. Calcd: C, 44.94; H, 5.99. Found: C, 45.41; H, 6.21.

9,10-Bis-*epi*-Stemoamide. A stirred solution of **22** (164 mg, 0.50 mmol) and AIBN (24 mg, 0.15 mmol, 0.3 equiv) in benzene (98 mL) was degassed by bubbling argon through the solution for 10 min. The mixture was heated at reflux, and a solution of Bu_3SnH (266 μL, 0.99 mmol, 2 equiv) in degassed benzene (3 mL) was added via a syringe pump over 2 h. The solvent was removed under reduced pressure, and the crude mixture was subjected to ^1H NMR and GC−MS analysis, which showed the presence of two diastereoisomers in a 2.5/1 ratio. The crude mixture was purified by flash chromatography on silica gel (gradient CH_2Cl_2/MeOH 100/0, 95/5) to afford 9,10-bis-*epi*-stemoamide (22.2 mg, 0.100 mmol, 20%) as a white amorphous solid. $C_{12}H_{17}NO_3$. MW: 223.27. R_f: 0.22 (CH_2Cl_2/MeOH 95/5). IR (film): 2944, 2861, 1780, 1692, 1446, 1202, 1094, 1051, 1018, 967, 662 cm^{-1}. ^1H RMN (400 MHz): δ 4.62 (ddd, J = 10.6, 7.5, 3.0 Hz, 1H), 4.19 (dt, J = 14.0, 4.5 Hz, 1H), 3.63 (m, 1H), 2.78 (ddd, J = 14.0, 10.6, 3.4 Hz, 1H), 2.62−2.23 (m, 5H), 2.15−2.07 (m, 1H), 2.00−1.80 (m, 3H), 1.70−1.55 (m, 1H), 1.39 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz): δ 177.9, 174.6, 80.7, 60.6, 50.8, 44.1, 39.1, 30.1, 28.9, 25.5, 24.0, 15.9. MS (EI) *m*/*z* (relative intensity): 223 ($M^{+\bullet}$, 87), 208 (41), 180 (44), 124 (30), 110 (34), 98 (100), 79 (22), 69 (33), 55 (26). MS (CI, CH_4) *m*/*z*: 224 (MH^+). HRMS (CI, CH_4): calcd 224.1287 (MH^+), found 224.1286.

Supporting Information Available: Experimental procedures and characterizations for all compounds, and copies of ^1H and ^{13}C NMR spectra for compounds **3**, **6**, **8**/**8′**, **10**/**10′**, **12**/**12′**, **13**/**13′**, **14**/**14′**, **15**/**15′**, **16**, **19**, **20**, **21**, **22**, and (±)-9,10-bis-*epi*-stemoamide. This material is available free of charge via the Internet at http://pubs.acs.org.

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