An Enantioselective Total Synthesis of (–)-Stemoamide

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Abstract: An enantioselective synthesis of (–)-stemoamide has been achieved in 14 steps starting from pyroglutamyl alcohol in ca. 7% overall yield. The key steps in the strategy are a conjugate addition of a vinyl copper reagent and a ring closing metathesis (RCM) reaction to form the seven-membered ring.

Key words: stemoamide, ring closing metathesis, conjugate addition, pyroglutamic acid

The stemona group of alkaloids has received considerable attention from synthetic chemists in the past decade (Figure 1).[1] Root extracts from stemona species have been used in traditional Chinese medicine to treat respiratory disorders.[2] Insecticidal, anti-feedant, and neuromuscular activities of some members of the stemona group have also been noted in the literature. Several groups have completed the synthesis of simple as well as more complex members of the stemona group.[3] A key feature of this class of alkaloids is the 1-azabicyclo[5.3.0]decane core (**5**) which is present in most members of this family. Five enantioselective total syntheses of stemoamide have been reported so far.[4] In this work we report an enantioselective synthesis of stemoamide that compares favorably in the total number of steps and overall yield to those reported in the literature.

Our strategy for the synthesis of stemoamide is outlined in Scheme 1. Our plan involved the conversion of the key tricyclic lactone **6** to the target which requires an epimerization of C-9 center using the precedence from Jacobi's work on stemoamide[4b] and C-10 methylation as described previously by Narasaka and co-workers.[4g] The final lactone ring would be constructed by iodolactonization of a bicyclic lactam, installing the correct stereochemistry at C-8. Other key steps in our strategy were the preparation of a bicyclic lactam from **7** via a ring closing metathesis (RCM) reaction. This precursor could be accessed through a *syn* selective conjugate addition of a vinyl fragment to **8**. (*S*)-Pyroglutamic acid would serve as the initial starting material similar to the several reported synthesis of stemoamide.

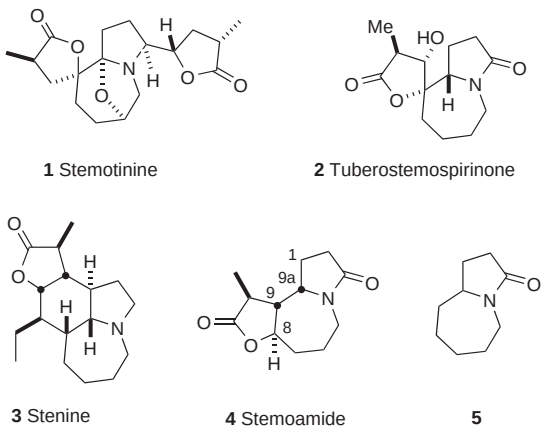
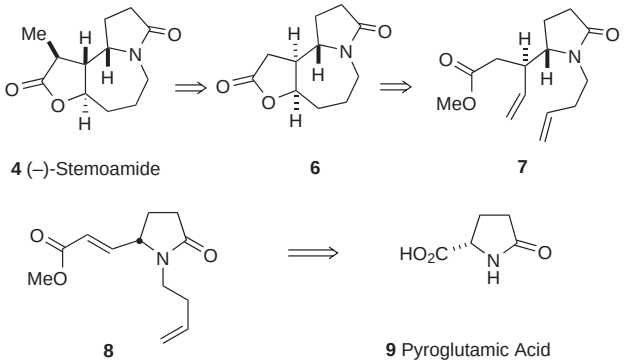


Figure 1 Stemona Alkaloids



Scheme 1 Retrosynthetic analysis

Our synthesis started from the inexpensive (*S*)-pyroglutamic acid **9** (Scheme 2). Esterification under standard conditions gave the known methyl ester **10**.[5] Initially, we attempted the alkylation of the lactam nitrogen of **10** with bromobutene under a variety of conditions. Although the alkylation was successful, extensive racemization of the chiral center was observed. To reduce the acidity of the methine hydrogen, the ester **10** was converted to the known primary alcohol **11** using sodium borohydride.[6] Protection of the primary alcohol as the TBS ether under standard conditions gave the known compound **12**.[7] Alkylation of the imide using bromobutene gave **13** in good yield.[8] Deprotection of the TBS ether using TBAF furnished the primary alcohol **14** in enantiomerically pure form. Swern oxidation under carefully controlled conditions gave the aldehyde which without purification was subjected to Wittig reaction with the preformed ylide.[9] The α,β-unsaturated ester **8** was obtained in good yield as a single *E*-isomer.

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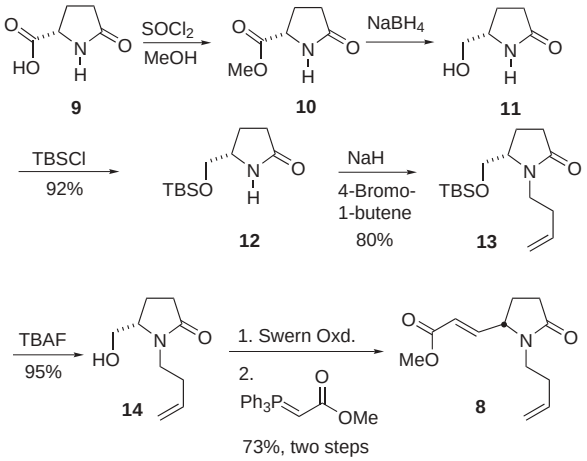
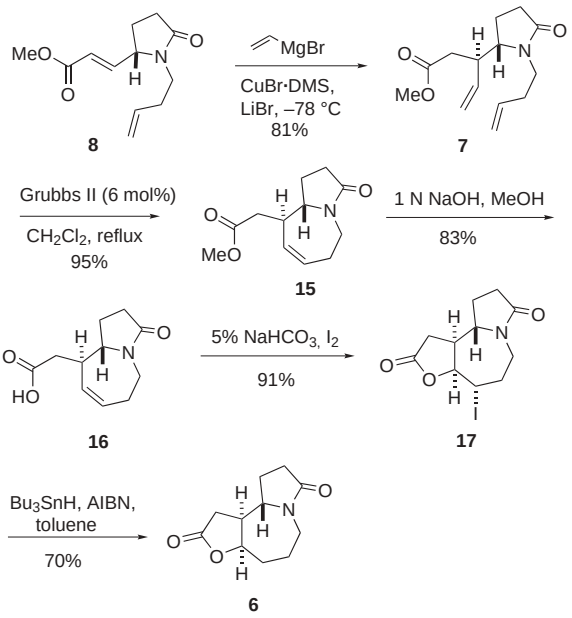


Scheme 2 Synthesis of the conjugate addition precursor **8**

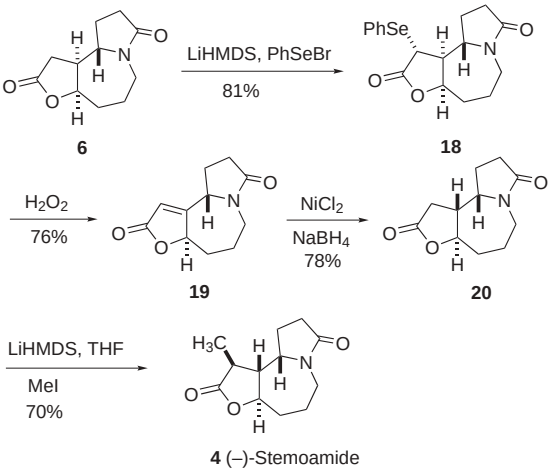
Highly *syn* stereoselective conjugate addition of copper reagents to γ-amino alkenoates have been reported in the literature.[10] This is in contrast to the high *anti* selectivity observed in conjugate additions to γ-alkoxy alkenoates.[11] With the intermediate **8** in hand, the introduction of the key vinyl group was undertaken (Scheme 3). Conjugate addition with the copper reagent derived from vinyl magnesium bromide and copper bromide gave **7** in excellent yield and as a single *syn* diastereomer.[12] The origins of the stereoselectivity with the γ-amino alkenoates are not completely apparent at the present time. However, re face addition in a Felkin–Anh model accounts for the observed *syn* selectivity for **7**. It should be noted that the configuration at the newly formed chiral center (C-9) is opposite to that of the target stemoamide.[13] The formation of seven-membered rings using RCM has been well established in the literature.[14] Ring closure of **7** using either Grubbs I or II catalyst gave the bicyclic lactam **15** in high yield. Hydrolysis of the ester gave the acid **16**. Iodolactonization under standard conditions produced the tricyclic lactone **17** in excellent yield. A detailed NMR structure analysis of **17** clearly established the relative stereochemistry at the four contiguous chiral centers. Thus the lactonization allows for the installation of the proper stereochemistry at C-8. Reduction of the iodolactone under radical conditions gave **6** in good yield over two steps.[15]

The next key step was epimerization of the stereocenter at C-9 (Scheme 4) by a three step protocol. Jacobi in his excellent work on the synthesis of stemoamide has shown that it is possible to obtain correct stereochemistry at C-9 by a stereoselective reduction.[4b] This is based on conformational analysis of the tricyclic core of the stemoamide.[16] Phenylselenation of **6** was achieved by treating it with LiHMDS followed by the addition of phenylselenyl bromide furnishing **18** in good yield.[17] Installation of the C9-C10 double bond was accomplished by selenoxide elimination providing **19** in good overall yield over two steps. The crucial reduction was accomplished using nickel chloride and sodium borohydride furnishing the known



Scheme 3 Synthesis of key tricyclic lactam **6**

lactone **20**[4a] with the proper configuration at C-9.[4b] Methylation of lactone **20** using a slight modification of the previously reported conditions of Narasaka[4g] gave stemoamide in 70% yield. The spectral and analytical characteristics of **4** were identical to those reported in the literature for (–)-stemoamide.[18] The overall yield of stemoamide is ca. 7% starting from pyroglutamyl alcohol **11**. The present synthesis compares favorably in yield and number of steps to those reported in the literature.[4]



Scheme 4 Completion of the synthesis of (–)-stemoamide

In conclusion we have developed an efficient synthesis of stemoamide, which highlights the use of stereoselective conjugate addition and ring closing metathesis as the key steps. The synthesis of other members of the stemona alkaloid family is underway in our laboratory.

Acknowledgment

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(12) **Procedure for Conjugate Addition**: Lithium bromide (2.59 g, 30.1 mmol, 6 equiv) and CuBr·DMS (3.059 g, 15.0 mmol) were placed in a dry round bottomed flask. THF (35 mL) was added to the solids and the reaction mixture was cooled to –78 °C. Vinyl magnesium bromide (30 mL, 0.977 molar solution in THF, 6 equiv) was added dropwise. After stirring for 30 min at the same temperature, ester **8** (1.1072 g, 5 mmol) in THF (10 mL) was added dropwise and the resultant solution was stirred at the same temperature for 10 min and at –40 °C for 50 min. The reaction was quenched with NH_4Cl solution and extracted with Et_2O repeatedly. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The concentrated residue was purified by silica gel column chromatography using EtOAc and hexane (EtOAc–hexane, 1:1) to give the ester **7** (1.02 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.69–1.76 (m, 1 H), 1.95–2.04 (m, 1 H), 2.25–2.39 (m, 4 H), 2.29 (d, *J* = 7.0 Hz, 2 H), 2.93 (m, 1 H), 3.05–3.11 (m, 1 H), 3.66 (s, 3 H), 3.75–3.84 (m, 2 H), 5.04 (d, *J* = 10.0 Hz, 1 H), 5.08 (d, *J* = 17.5 Hz, 1 H), 5.18 (dd, *J* = 13.5, 3 Hz, 2 H), 5.73 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5, 30.4, 31.7, 32.4, 39.9, 41.3, 52.1, 60.0, 117.3, 117.9, 135.3, 136.7, 172.7, 175.6. IR (neat): 1733, 1674 cm^{-1}. $[\alpha]_D^{25}$ +17.3 (*c* = 1.0, MeOH). HRMS: *m*/*z* calcd for $C_{14}H_{21}NO_3Na^+$: 274.1413; found: 274.1410. The stereochemistry at C-9 was unambiguously established at a later stage (compounds **15** and **17**).

(13) Interestingly, conjugate addition to the corresponding *Z*-ester gave a 2:1 mixture of diastereomers with **7** as the major product (data not shown).

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(15) **Preparation of the Tricyclic Lactam 6**: The iodolactone **17** (0.748 g, 2.2 mmol) was dissolved in degassed toluene (75 mL) in a two-neck round-bottomed flask fitted with a reflux condenser and a rubber septum. Tributyltin hydride (0.722 mL, 2.68 mmol) was added and the reaction heated to 80 °C. A solution of AIBN (60 mg) in toluene (5 mL) was added to the reaction mixture four times with the interval of 1 h. The resultant solution was refluxed for 10 h. The solvent was removed and the residue was chromatographed over silica gel to give **6** as a highly viscous liquid that solidified upon cooling (0.321 g, 70%); mp 42–43 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51–1.60 (m, 2 H), 1.70 (q, *J* = 10.5 Hz, 1 H), 1.83–1.85 (m, 1 H), 2.02–2.08 (m, 1 H), 2.36–2.41 (m, 4 H), 2.47–2.53 (m, 1 H), 2.60–2.70 (m, 1 H), 2.76–2.87 (m, 1 H), 4.0 (dt, *J* = 6.0, 10.5 Hz, 1 H), 4.11–4.14 (m, 1 H), 4.27 (dt, *J* = 3.0, 10.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.9, 25.7, 30.8, 31.2, 34.8, 40.4, 45.1, 56.3, 80.0, 174.3, 174.9. $[\alpha]_D^{25}$ –91.9 (*c* = 1.0, $CHCl_3$). HRMS: *m*/*z* calcd for $C_{11}H_{15}NO_3Na$: 232.0944; found: 232.0940.

(16) Also see ref. 4c for a similar reduction and establishment of stereocenter at C-9 and C-10.

(17) Lactone **6** could also be methylated to provide C-9, C-10 diepi stemoamide (data not shown).

(18) Mp: 185–186 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 6.9 Hz, 3 H), 1.50–1.58 (m, 2 H), 1.72 (quint, *J* = 10.7 Hz, 1 H), 1.85–1.90 (m, 1 H), 2.0–2.10 (m, 1 H), 2.38–2.45 (m, 4 H), 2.60 (dq, *J* = 6.9, 12.5 Hz, 1 H), 2.65 (dd, *J* = 12.3, 14.1 Hz, 1 H), 3.99 (dt, *J* = 10.8, 6.3 Hz, 1 H), 4.16 (m, 1 H), 4.20 (dt, *J* = 3.1, 10.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.5, 25.6, 30.5, 34.8, 37.3, 40.2, 52.7, 55.8, 77.6, 174.0, 177.3. IR (neat): 1768, 1681 cm^{-1}. $[\alpha]_D^{25}$ –191.6 (*c* = 0.5, MeOH). {Lit. $[\alpha]_D^{25}$ –183.5 (*c* = 1.36, MeOH);[4b] $[\alpha]_D^{30}$ –219.3 (*c* = 0.5, MeOH);[4d] $[\alpha]_D$ –181.6 (*c* = 0.89, MeOH)}.[4e] HRMS: *m*/*z* calcd for $C_{12}H_{17}NO_3Na^+$: 246.1100: found: 246.1099.