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Formal synthesis of (−)-stemoamide using a useful epimerization at C-8

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ABSTRACT

The formal synthesis of (−)-stemoamide was achieved starting from L-pyroglutamic acid. The key steps used are the allylation using $BF_3{\cdot}OEt_2$, ring closing metathesis, allylic oxidation and a novel epimerization at C8.

The ancient people had great sense of using plant extracts for the treatment of various diseases, based on their traditional knowledge of these plants possessing biologically active molecules responsible for cure. One such root extract used for the treatment of tuberculosis, pertussis and throat infections in traditional Chinese and Japanese medicines belongs to the *Stemonaceae* family.[1] The root extracts of *Stemonaceae* family consist of more than hundred and thirty stemona alkaloids.[2] The common structural feature encountered in stemona alkaloids is the presence of perhydropyrrolo azepine as well as γ-butyrolactone core. Taking into account the interesting structure and important biological activity of stemona alkaloids, there is a need to develop novel synthetic routes to this class of compounds.[1]

(−)-Stemoamide **1** (Fig. 1), one of the stemona alkaloids was isolated by Xu and co-workers in 1992 from *Stemona tuberosa* Lour and related stemona species.[3] Amongst the stemona alkaloid family, (−)-stemoamide is the simplest and structurally attractive molecule.[4] To date eight different routes are reported for the synthesis of (−)-stemoamide, so there is a considerable scope for its synthesis.[5] Besides this, ten various other strategies are reported for the synthesis of stemoamide, six of them describe different routes leading to racemic syntheses while rest of them describe the syntheses of its unnatural isomers. Jacobi et al. in their seminal manuscript[5c] disclosed the interesting steric bias of the tricyclic skeleton of stemoamide leading to a high degree of diastereoselectivity by computational studies which was backed by experimental observations and it was attributed to the thermodynamic stabilization of stemoamide structure. Herein we describe our efforts towards the enantioselective synthesis of (−)-stemoamide starting from L-pyroglutamic acid.

According to our retrosynthetic plan (Scheme 1), the key intermediate is butenolide **2**. Elaboration of the intermediate **2** to **1** is well documented.[5f,g] In turn our focus was the construction of butenolide ring **2** based on our previously reported strategy for butenolide synthesis,[6] which includes the Reformatsky reaction on ketone **5** to furnish the corresponding hydroxy ester which on dehydration furnishes β,γ-unsaturated ester which on dihydroxylation and treatment with acid would provide butenolide. The ketone **5** could be constructed by two routes, one by taking advantage of RCM strategy and another route by taking advantage of Grignard reaction on aldehyde **10**. The di-allylated precursor **6** could be constructed from L-pyroglutamic acid **11**.

Our synthesis started from L-pyroglutamic acid **11** (Scheme 2) wherein the *N*-allyl alcohol **12** was prepared using the reported method with no loss in chirality.[7] The resulting *N*-allyl alcohol **12** was oxidized to aldehyde **7** using IBX in refluxing ethyl acetate. The crude aldehyde **7**, as such, was subjected to allylation using allyltrimethylsilane and TBAF in THF but we were unable to get di-allylated product **6** in good yields despite modifications in the

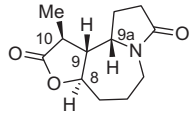

Figure 1. (−)-Stemoamide **1**.

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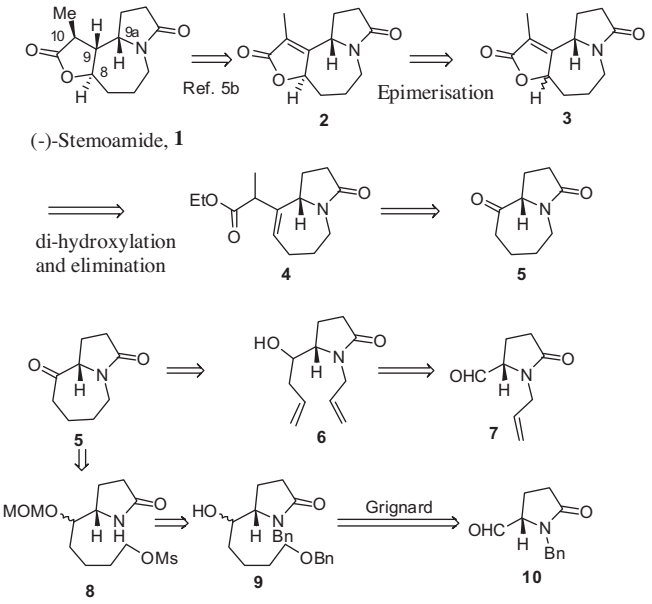
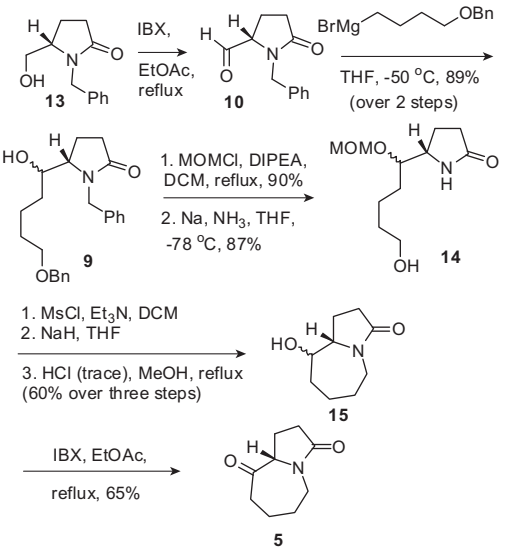


Scheme 1. Retrosynthetic analysis of (−)-stemoamide.

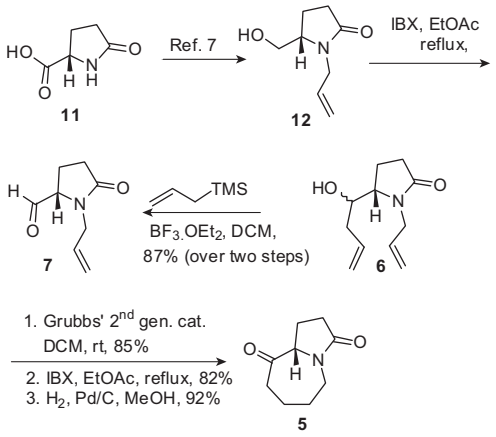


Scheme 3. Alternate route to ketone **5**.

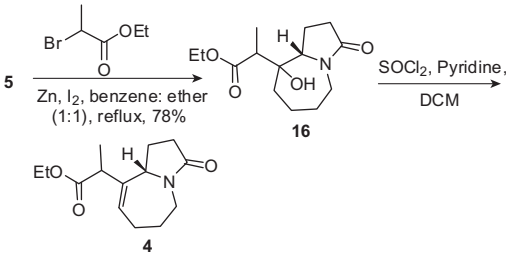
amounts of allyltrimethylsilane and of TBAF. However, by performing the reaction under Lewis acidic conditions employing $BF_3.OEt_2$ as catalysts in DCM we got the di-allylated product **6** in 87% yield. The ^1H NMR of di-allylated compound **6** showed it to be a mixture of diastereomers, which did not matter to us because the alcohol functionality in **6** was to be oxidized at a later stage.

The di-allylated product **6** was subjected to RCM reaction using Grubbs' 1st generation catalyst (2 mol %) in DCM, which resulted in cyclic olefin product but low yields (34%) were obtained at room temperature as well as under reflux conditions. Varying the amount of Grubbs' catalyst up to 8 mol % also resulted in unsatisfactory yield, up to a maximum of 40%. However switching over to the use of Grubbs' 2nd generation catalyst (2 mol %) in DCM at room temperature furnished good yield (85%) of ring closed product.[8] The subsequent oxidation of alcohol using IBX in ethyl acetate under reflux conditions and reduction of double bond by hydrogenation using 10% Pd over carbon in methanol under hydrogen (60 psi) provided ketone **5** in 92% yield. Ketone **5** was also prepared by another route (Scheme 3). Alcohol **13** was prepared according to the reported procedure from L-pyroglutamic acid.[9] Alcohol **13** was oxidized using IBX in ethyl acetate under reflux conditions to provide aldehyde **10** with no loss in chirality. The required Grignard reagent was prepared from 4-benzyloxybutyl bromide and activated Mg in THF. The crude aldehyde **10** was initially treated with 2 equiv of Grignard reagent at room temperature in THF which resulted in complex reaction mixture. After optimization of reaction conditions, the Grignard reaction was performed at −50 °C in the presence of THF as the solvent, furnishing alcohol **9** in 89% yield. Alcohol **9** was reacted with methoxymethyl chloride in the presence of Hünig's base in DCM under reflux condition to afford the corresponding MOM ether in 90% yield. Subsequently the MOM protected compound was subjected to Birch reduction using Na and ammonia in THF at −78 °C for one hour to provide amido alcohol **14** in 87% yield. Mesylation of **14** was carried out using MsCl and triethylamine in DCM at room temperature. The mesyl compound was then subjected to react with NaH in THF to provide cyclized compound which was subsequently subjected to MOM deprotection using trace amount of conc. HCl in methanol under reflux conditions to provide alcohol **15** in 60% yield over three steps. The bicyclic alcohol **15** was oxidized to ketone **5** using IBX (2 equiv) in ethyl acetate under reflux condition for 3 hours, in 65% yield.

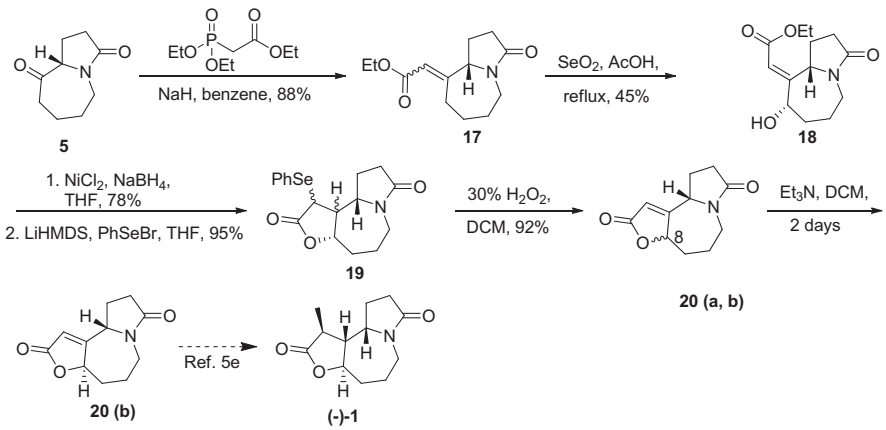
Ketone **5** was subjected to Reformatsky reaction (Scheme 4) using ethyl 2-bromopropionate in the presence of zinc and catalytic iodine to give alcohol **16** in 78% yield almost as a single diastereomer as judged by the examination of the spectral data (^1H NMR, ^{13}C NMR). The next job was to eliminate the hydroxy group to obtain the alkene **4**. We subjected the alcohol **16** to elimination using thionyl chloride and pyridine in DCM to furnish isomeric mixture of olefins including the desired olefin **4**.



Scheme 2. Synthesis of ketone **5**.



Scheme 4. Synthesis of **1**.



Scheme 5. Synthesis of **1** using alternate route to proposed plan.

Alkene **4** was obtained as an inseparable mixture of 3 isomeric olefins in equal proportions, which was confirmed by LCMS although the exact identity of the olefins could not be rigorously established.[10] In spite of several modifications, we were not able to obtain the required alkene **4** exclusively and it was very difficult to proceed with the mixture.

The undesired results obtained during elimination forced us to change our route to (−)-stemoamide **1**. The ketone **5** was subjected to Horner-Wadsworth–Emmons reaction (Scheme 5) using triethyl phosphonoacetate, to furnish α,β-unsaturated ester **17** in 88% yield as a (4:1) mixture of olefins with *E* isomer predominating. This was confirmed by X-ray analysis of the corresponding acid **17a** (Fig. 2).[11]

It was surmised that the butenolide **20** could be readily obtained by performing allylic oxidation on substrate **17** according to the literature report.[12] Accordingly we carried out allylic oxidation using selenium dioxide under reflux conditions in acetic acid, but unfortunately instead of butenolide **20**, the uncyclized hydroxy ester **18** was obtained as a single diastereomer. We were unable to isolate any other isomeric product from the remaining intractable residue.[13] Failure to obtain butenolide was attributed to the *Z* configuration at double bond in hydroxy olefin **18,** in which ester is away from the hydroxy group, which indeed was later confirmed by single crystal X-ray analysis of **18** (Fig. 3).[14] The isomerization of the olefin could be explained based on the literature precedence which involves [2,3]-rearrangement of the seleno ester intermediate during allylic oxidation in acidic conditions.[15] It may be pointed out that the hydroxy group installed had the opposite stereochemistry than what is required for (−)-stemoamide. Hydroxy olefin **18** was treated with various reagents like PTSA, H_2SO_4, HCl, thiophenol-triethylamine and thiophenol-sodium hydride but none of the above conditions resulted in the formation of butenolide **20 (b)**.

As we were unable to transform the hydroxy ester **18** directly into butenolide **20**, we had to take a circuitous route. After the unsuccessful attempts to cyclize the hydroxy olefin **18**, we reduced the double bond using $NiCl_2$:$NaBH_4$ in THF which furnished cyclized butyrolactone product in 78% yield. But the stereochemistry of cyclized product disappointed us because the NMR spectrum showed it to be a diastereomeric mixture in which C8 was not of desired stereochemistry.

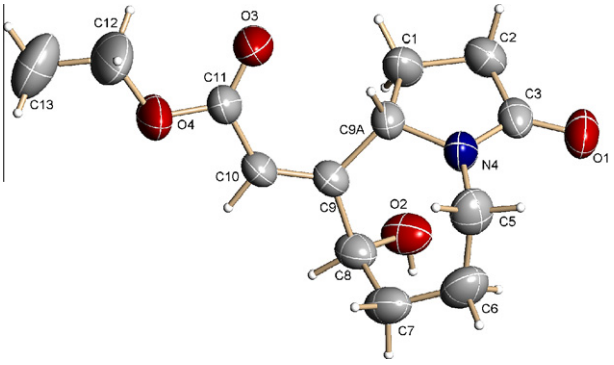


Figure 3. The X-ray structure of ester **18**.

In order to fix these two centres, we converted cyclized product into α-phenyl selenolactone derivative using LiHMDS and PhSeBr in THF to give selenyl compound **19** in 95% yield, according to Sibi's protocol.[5e] The selenolactone **19** was subjected to elimination using hydrogen peroxide in DCM at 0 °C, to furnish butenolide **20 (a, b)** in 92% yield. The butenolide **20 (a, b)** was obtained as a diastereomeric mixture in the ratio 70:30 which was evident from ^{1}H NMR spectrum. The major diastereomer was with undesired stereochemistry. Although compounds **19** and **20 (a, b)** were the mixture of diastereomers, they were almost homogenous by TLC and were carried forward to eventually obtain butenolide **20(b)** as a single diastereomer.

Careful observation revealed that these two diastereomers of **20(a,b)** have a very small difference in R_f values. We treated this diastereomeric mixture with triethylamine in DCM and to our delight we observed that the concentration of the faster moving (less polar) spot increased when the reaction was monitored by TLC. After prolonging this reaction by stirring the reaction mixture for almost two days, we observed that the mixture was completely transformed in to the desired butenolide **20(b)**.

After characterization, it was confirmed that the observed product was the desired diastereomer butenolide **20(b)** whose melting point, spectral data and $[\alpha]_D$ value agreed with those reported.[5f] Hence for the first time we have successfully converted the

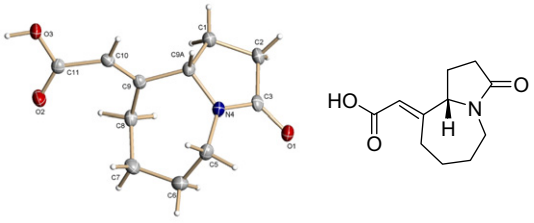


Figure 2. The X-ray structure of acid **17a**.

diastereomeric mixture **20 (a, b)** into the required isomer **20(b)** in good yields.[16] The conversion of butenolide **20(b)** into (−)-stemoamide is well documented in the literature in two steps,[5g] hence this constitutes the formal total synthesis of (−)-stemoamide. By performing this sequence of reactions we were able to convert ketone **5** into butenolide **20(b)** in 27% overall yields.

In conclusion, the formal total synthesis of (−)-stemoamide was achieved by taking advantage of RCM and allylic oxidation in 11 steps in 15% overall yield. The alternate route to seven membered ring construction was developed using Grignard reaction and base induced cyclization to furnish butenolide **20(b)** in 14 steps in 11% overall yield. Complete novel epimerization of **20(a, b)** to expected isomer **20(b)** was achieved successfully.

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11. CCDC 866111 (**17a**) contains the Supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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13. *Allylic oxidation, synthesis of **18***
To the α,β-unsaturated ester **14** (400 mg, 1.7 mmol) in acetic acid (10 mL), was added selenium dioxide (284 mg, 2.5 mmol) and the resulting reaction mixture was heated at reflux for 5 h. The reaction mixture was filtered on celite and the residue was washed with ethyl acetate (50 mL). The collected filtrates were concentrated in vacuo and purified using flash chromatography (EtOAc) to afford hydroxy compound **15** (272 mg, 45%) as a crystalline solid (mp 104–105 °C). IR ($CHCl_3$) ν_{max}: 3367, 2925, 2800, 1706, 1663, 1402, 1223, 1175 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (s, 1H), 5.41 (t, J = 7.2 Hz, 1H), 4.60 (d, J = 6.2 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.11 (br d, J = 14 Hz, 1H), 2.34–2.65 (m, 4H), 2.20–2.25 (m, 1H), 1.88–2.09 (m, 2H), 1.54–1.61 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 165.6, 163.9, 117.5, 77.2, 60.4, 60.2, 42.8, 35.3, 30.3, 25.6, 21.9, 14.2; ESIMS (m/z): 254 $(M+H)^+$, 276 $(M+Na)^+$.
14. CCDC 866112 (**18**) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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16. *Epimerization of **20**(**a**, **b**) to **20**(**b**).*
To the diastereomeric mixture of butenolide **20(a, b)** (30 mg, 0.15 mmol) in anhydrous DCM (5 mL), was added triethylamine (0.04 ml, 2.9 mmol) and the reaction mixture was stirred for 2 days. The reaction mixture was concentrated in vacuo and the residue purified using flash chromatography (2:98 MeOH:EtOAc) to afford diastereomerically pure butenolide **20(b)** (24 mg, 80%) as a white solid (mp 158–159 °C, lit.[5g] mp 157–158 °C) $[\alpha]_D^{25}$ - 227 (, 0.4 $CHCl_3$), lit.[5g]-$[\alpha]_D^{20}$ – 224 (*c*, 0.4 $CHCl_3$), IR ($CHCl_3$) ν_{max}: 2928, 2850, 1753, 1665, 1454, 1223, 911, 750 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (s, 1H), 5.00–5.03 (m, 1H), 4.77–4.81 (m, 1H), 4.29–4.32 (m, 1H), 2.49–2.58 (m, 5H), 1.84–1.94 (m, 2H), 1.68–-1.76 (m, 1H), 1.40–1.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 174.1, 171.7, 115.9, 82.9, 58.1, 43.4, 34.5, 30.2, 27.7, 25.7; ESIMS (m/z): 208 $(M+H)^+$, 230 $(M+Na)^+$.