Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 673

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COMMUNICATION

Efficient total synthesis of (–)-stemoamide†

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Received 8th October 2010, Accepted 19th November 2010
DOI: 10.1039/c0ob00850h

An efficient diastereoselective synthesis of (–)-stemoamide has been accomplished from a pyroglutamic acid derivative in eight steps and with 24% overall yield. The synthesis features an intramolecular samarium diiodide-promoted 7-*exo-trig* cyclization of a ketyl radical generated from the corresponding aldehyde.

Stemoamide **1**, isolated from the roots and rhizomes of Stemonaceous plants together with its related polycyclic alkaloids, stemonine **2**, stenine **3** and stemospironine **4**, is the structurally simplest alkaloid among the *Stemona* class of natural products (Fig. 1).[1] The roots of *Stemona tuberosa* Lour and related *Stemona* species (Stemonaceae) are used in Chinese traditional medicine as antitussive agents[2] and also as insecticides and anthelmintics.[3]

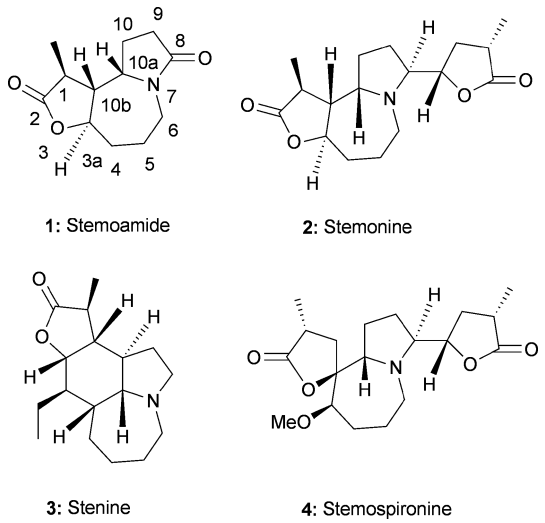

Fig. 1 Structures of typical *Stemona* alkaloids.

The structure of **1** was determined mainly by spectroscopic methods to contain a γ-butyrolactam that forms part of a pyrrolo[1,2-*a*]azepine ring system fused on a γ-butyrolactone ring with four contiguous stereogenic centers. Due to their interesting biological properties as well as their structural diversity, this class of natural products has received considerable attention in recent years, and the first total synthesis of **1** was accomplished by Williams and co-workers in 1994.[4] Thereafter several syntheses and synthetic approaches to **1** have appeared sequentially, with newly developed synthetic methods and strategies having been applied to construct its core skeleton as the target molecule.[5] The crucial step for the synthesis of **1** lies in the construction of a tricyclic ring system by controlling the stereogenic centers at the 1, 3a, 10a and 10b positions. We thought that the most straightforward way to construct the desired stereochemistry at the 10a position must be the use of (*S*)-pyroglutamic acid as the starting material. Construction of a γ-butyrolactone fused on the seven-membered ring could be achieved by a carbon–carbon bond formation between 3a and 10b (stemoamide numbering system as depicted in Fig. 1) by exploitation of an intramolecular samarium diiodide-promoted conjugate addition of a ketyl radical[6] generated *in situ* from a corresponding aldehyde, to an α,β-unsaturated ester, followed by a stereoselective installation of a methyl group at the 1-position at the last stage of the synthesis. Our retrosynthetic route for **1** is depicted in Scheme 1. The synthetic strategy we planned here would require relatively short reaction sequences compared to those in previous works.[5]

Thus, the requisite key aldehyde (**11**) was prepared starting from the known lactam (**5**)[5d–f] as follows. Alkylation of the lactam (**5**) with 2-(4-bromobutoxy)tetrahydro-2*H*-pyran[7] in the presence of NaHMDS at −15 °C in DMF afforded an alkylation product (**6**) in 88% yield. After removal of the silyl group of **6** upon treatment with ammonium fluoride in MeOH under reflux, the resulting primary alcohol **7** was converted to the aldehyde (**8**) by Swern oxidation. Wittig reaction of **8** with methyl (triphenylphosphoranylidene)acetate in acetonitrile at ambient temperature gave the (*E*)-olefin (**9**), in 82% yield from **7**, which on treatment with *p*-TsOH in MeOH furnished the primary alcohol (**10**) in 92% yield. Oxidation of the alcohol (**10**) by Swern oxidation provided the desired aldehyde (**11**) in 85% yield.

With the pivotal precursor in hand, we attempted a samarium diiodide-promoted carbon–carbon bond forming reaction *via* a 1,4-conjugate addition of a ketyl radical generated *in situ* from aldehyde **11** under various reaction conditions. First, an intramolecular coupling of aldehyde **11** was conducted with 5.0 equivalents of samarium diiodide in THF in the presence of 5.0 equivalents of MeOH as the proton source at 0 °C for 3 h to give an inseparable diastereoisomeric mixture of coupling products **12** and **13** in 60% yield (Scheme 2).

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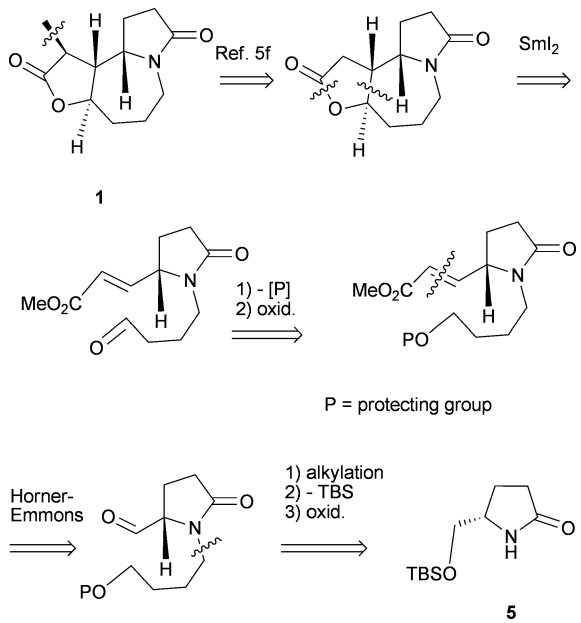
† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization data for compounds **6–18**, ^{1}H NMR and ^{13}C NMR spectra for the key compounds **6**, **7**, **9**, **10**, **11**, **15**, and **16**, and also **1**. See DOI: 10.1039/c0ob00850h



Scheme 1 Retrosynthetic route for (–)-stemonamide **1**.

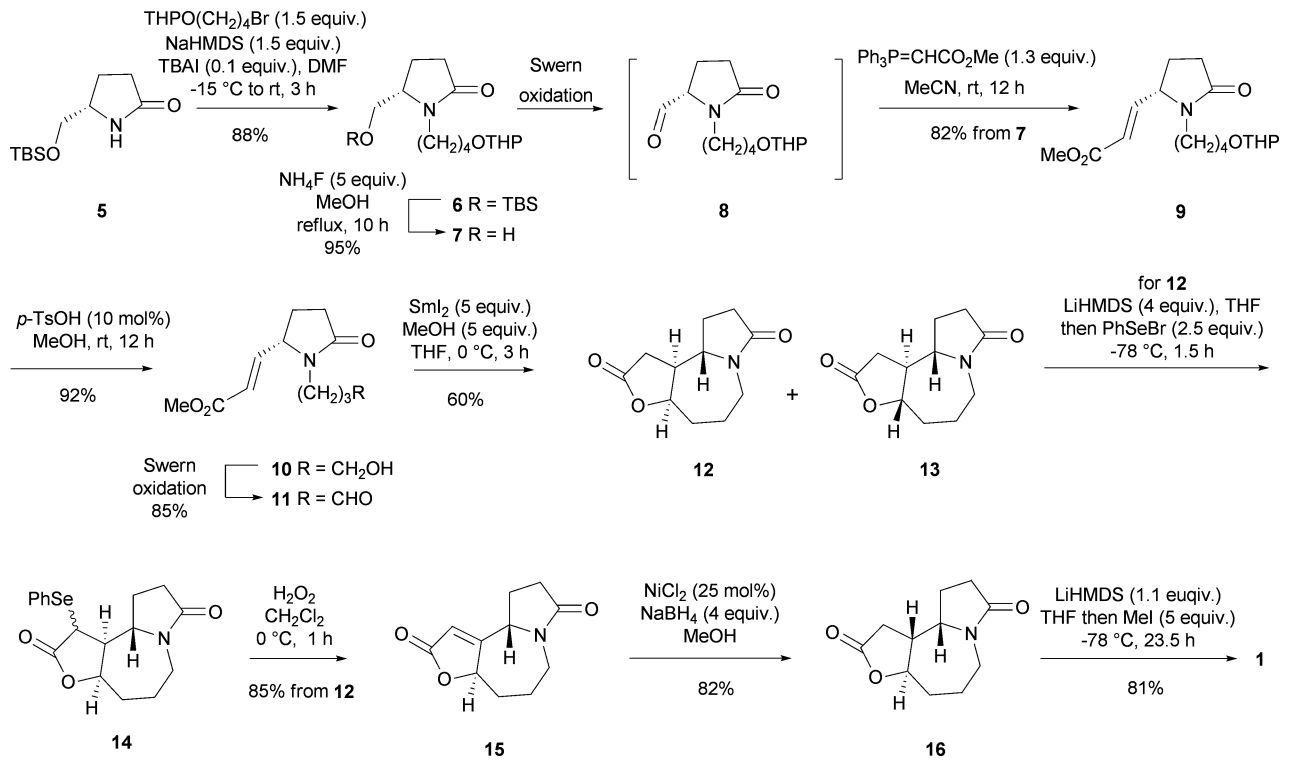
By careful examination of their NMR spectra, the structures of the products were assumed to be **12**[5d] and **13**[5j,5k] with a ratio of 1 : 0.9. To confirm their structures unambiguously, partially separated **12** was treated with phenylselenyl bromide in the presence of LiHMDS in THF at –78 °C for 2 h to give selenide **14**, which upon subsequent treatment with 30% hydrogen peroxide gave butenolide **15** as an oxidative elimination product in 85% yield. Spectroscopic data of **15** including its specific optical rotation, mp 156–157 °C (lit.,[5f] mp 157–158 °C); $[\alpha]_D$ –204 (*c* 0.4, $CHCl_3$) {lit.,[5f] $[\alpha]_D$ –224 (*c* 0.4, $CHCl_3$)} were comparable to those reported in the literature.[5f] Further transformation of **15** to stemoamide **1** was achieved *via* the known γ-butyrolactone **16** by reduction of its carbon–carbon double bond with nickel(II) chloride and sodium borohydride and subsequent stereoselective methylation of **16** with methyl iodide according to the literature procedure.[5f] Again, spectroscopic data of those compounds were similar to those reported in the literature.[5f]

Thus, this synthesis constitutes an alternative total synthesis of (–)-stemoamide.

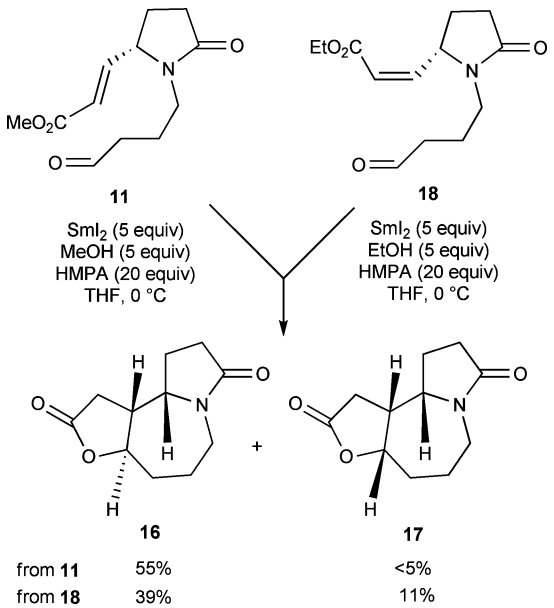
In this synthesis, however, the expected diastereoselectivity could not be obtained in the key cyclization step. Fortunately, when a samarium diiodide-promoted carbon–carbon bond forming reaction was carried out with 5.0 equivalents of samarium diiodide in THF in the presence of HMPA at 0 °C for 3 h, the desired lactone **16** was isolated in 55% yield, $[\alpha]_D$ –97.8 (*c* 0.3, $CHCl_3$) {lit.,[5f] $[\alpha]_D$ –94.0 (*c* 0.4, $CHCl_3$)}, together with a trace amount of the diastereoisomer (**17**).‡ Again, a stereoselective methylation of **16** afforded stemoamide **1**.

Similar stereocontrol in different reactions depending upon the reaction conditions was also observed by several groups during samarium diiodide-promoted coupling reaction of carbonyl compounds in the presence or absence of HMPA.[8] For further investigation of the stereoselectivity, the (*Z*)-isomer of olefin **18**, prepared from **5** in five steps involving Ando's variant of the Wittig reaction[9] as a key step, was subjected to the coupling reaction (Scheme 3).

Again, the desired compound **16** was obtained by the reaction of **18** with samarium diiodide in the presence of HMPA in 39% yield, as the major coupling product. On the other hand, a similar



Scheme 2 Synthesis of stemoamide by a SmI_2-promoted coupling of **11** in the absence of HMPA.



Scheme 3 SmI_2-promoted coupling of **11** and **18** in the presence of HMPA.

reaction of **18** in the absence of HMPA furnished a mixture of **12** and **13** in moderate yield, with a ratio of 1 : 0.7. These results clearly indicated that the stereochemistry at the carbon–carbon double bond did not affect the stereoselectivity of the product(s) for the samarium diiodide-promoted coupling and suggested that the chelation transition model usually observed[6m,n] in the absence of HMPA might not be involved in the coupling reaction in the presence of HMPA.

Although the precise reaction mechanism remained unclear, the observed stereoselectivity would be rationalized by assuming that the coupling reaction in the presence of HMPA proceeded through the most sterically favored diradical transition state (**TS-A**), where two functional groups were located in an energetically preferable diequatorial-like orientation as depicted in Fig. 2. The strong redox potential of samarium diiodide in the presence of HMPA[10] would make it possible to generate diradicals, as the key intermediate, as suggested by Matsuda and co-workers.[8a]

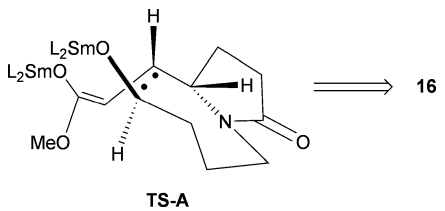


Fig. 2 Plausible transition state for the stereoselectivity.

In summary, we were able to establish an efficient stereoselective synthesis of (–)-stemoamide **1** starting from the known lactam **5**, readily accessible from pyroglutamic acid, in eight steps and with 24% overall yield. Our synthesis features a samarium diiodide-promoted 7-*exo*-*trig* cyclization of a ketyl radical generated *in situ* from the corresponding aldehyde. The strategy developed here is applicable to the synthesis of other types of alkaloids including the *Stemona* class of natural products.

This research was supported financially in part by a grant for The Open Research Center Project and a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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‡ Compound (**17**) could not be isolated in pure form, unfortunately, due to the small amount available.

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