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Cascade cyclization triggered by imine formation. Formal synthesis of the alkaloid (±)-stemoamide and its 9a-epimer

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ABSTRACT

A concise formal synthesis of stemoamide (**1**) and its 9a-epimer **14** in 5 steps is described featuring a cascade cyclization triggered by imine formation. A good selectivity for either epimer is readily accomplished by variation of the ester (**9b** or **9a**, respectively) and the reaction conditions.

Extracts from plants belonging to the Stemonacea family have been used in Southeast Asia's folk medicine for a long time. In particular, extracts from the roots of *Stemona tuberosa*, *Stemona sessilifolia,* and *Stemona japonica* have been prescribed in China and Japan for therapeutic purposes and also used as domestic insecticides, and they are still readily available at local markets.[1]

Stemona alkaloids comprise a group of approximately 170 polycyclic compounds[2] with most of them displaying a characteristic pyrrolo[1,2-*a*]azepine, pyrido[1,2-*a*]azepine or, as recently found, a pyrido[1,3-*a*]azepine core. Additionally, some other structural features such as the presence of a pyrido[1,2-*a*]azonine[3] or indolizidine[4] have recently been described.

Stemoamide (**1**, Fig. 1) was first identified by Xu and co-workers in 1992 as a secondary metabolite from *S. tuberosa*.[5] Due to its novel architecture and its stature as one of the simplest representative members of this class of alkaloids, it attracted the attention of synthetic chemists and it has been prepared several times in the past, with most approaches focusing on the construction of the ring junction at C9a, followed by diastereoselective transformations to set in place the remaining stereogenic carbons.[6]

Our retrosynthetic analysis of stemoamide (**1**) relies on a stereoselective reduction/lactamization of imine **B**, followed by a

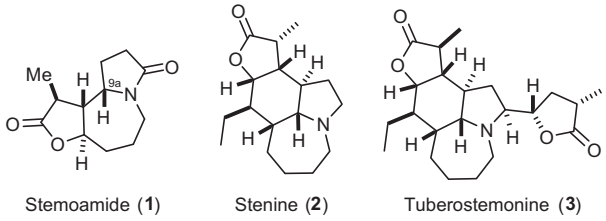

Figure 1. Structures of representative Stemona alkaloids.

precedented diastereoselective methylation. Imine **B** was assumed to form after amine deprotection in **C** which, in turn, would be prepared via a stereoselective Michael addition of nitroester **E** to furanone **D** (Scheme 1).

Intermediates **9a**,**b** were prepared via a straightforward Mukaiyama-Michael addition of commercially available 2-(trimethylsilyloxy)furan (**4**) to acrolein, catalyzed by pyrrolidine in the presence of 2,5-dinitrobenzoic acid, to provide aldehyde **5** in 96% yield.[7] While our work was in progress, Qiu and co-workers reported the addition of 2-methyl-γ-butenolide to acrolein catalyzed by dimethylamine hydrochloride in 67% yield.[6m]

The nitrogen atom present in the desired alkaloid was inserted via reductive carbamoylation to provide carbamate **6** in 85% yield according to the procedure by Dubé and co-workers.[8] DBU-mediated Michael addition of nitroesters **7a**,**b** to **6**, followed by a

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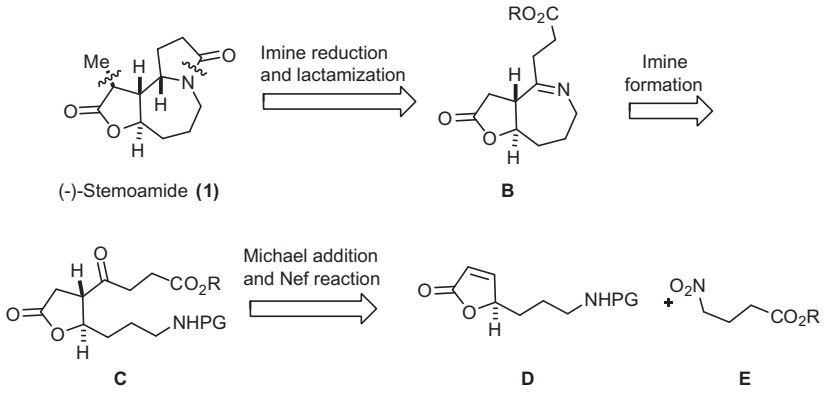


Scheme 1. Retrosynthetic analysis.

Nef reaction, furnished compounds **9a**,**b** in good overall yields (Scheme 2). The *trans*-stereochemistry was assigned based on our previously published results[9] and for highest yields in the Nef reaction the mild reaction conditions described by Burés and Villarasa were required.[10]

Esters **9a** and **9b** were subjected to hydrogenolysis in the presence of $Pd(OH)_2/C$ as catalyst and 2 or 4.5 atm of hydrogen pressure in ethyl acetate in order to set the stage for a tandem nitrogen deprotection, imine formation followed by a stereoselective hydrogenation which was expected to deliver the hydrogen from the less encumbered *Re*-face of the imine intermediate to provide the stemoamide core. To our surprise, when methyl ester **9a** was subjected to the hydrogenolysis conditions mentioned above, a 5:1 mixture of tricyclic lactams **10** and **11** (epimers at C-9a) was obtained in 45% overall yield (after four transformations). Since both products were already described in the literature.[6i,11] the diastereomeric ratio was easily determined by ^{1}H NMR analysis (see Supporting information).

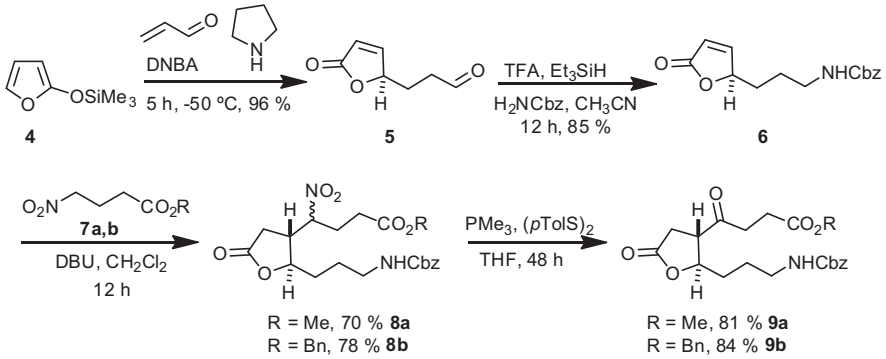
In contrast, when benzyl ester **9b** was submitted to the same reaction conditions (4.5 atm of H_2), lactam **11** was obtained as the major isomer, albeit in a low diastereomeric ratio (1:1.4) (Scheme 3). Fortunately, when the reaction was carried out at 10 atm of hydrogen pressure under otherwise identical experimental conditions, the preference of ester **9b** to afford tricyclic lactam **11** increased (dr = 1:3, Table 1).

Intrigued by these results, we explored a small series of ester analogs in the hydrogenolysis/cyclization/reduction manifold (Table 1). The bulky 2,6-dimethylphenyl ester **9c** (entry 2) led to a slight decrease in the formation of the desired isomer while α- and β-branched alkyl esters **9d** and **9e** provided either no selectivity (entry 3) or tricyclic lactam **10** as the main product (entry 4). Based on these results, we decided to investigate the nature of the solvent and the catalyst on the diastereoselectivity of this reaction sequence using benzylic ester **9b** as the substrate (Table 2).

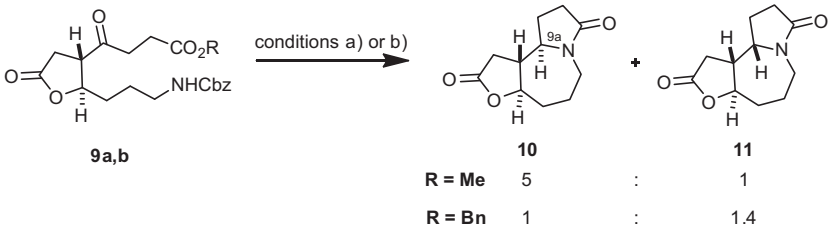
Entries 1–3 (Table 2) provide the results for reactions carried out in different solvents using $Pd(OH)_2/C$ as the catalyst and 10 atm of H_2. Under these conditions, the best ratio in favor of isomer **11** was achieved when trifluoroethanol was employed as solvent (entry 3, dr = 1:10). In contrast, the use of PtO_2/C, Crabtree's catalyst[12] or Ru/C was not effective in promoting the cascade of events leading to the formation of the stemoamide core. In the presence of platinum(IV) oxide, the secondary alcohol **13** was the only isolated product (80% yield). Therefore, the best experimental conditions (entry 3) afforded tricyclic lactam **11** in 27% overall yield (four steps) as a 1:10 diastereomeric mixture, together with 31% of aminoacid **12**.

The influence of the nature of the remote ester in the diastereoselectivity of the imine reduction was also investigated via a computational analysis at the PCM/M062X/6-311+G**//M062X/6-31G* level of theory either in ethyl acetate or trifluoroethanol (TFE) as solvents. Figure 2 shows the most stable conformations located for each system, all displaying a half-chair topology in the 7-membered ring.

In the case of imine **B-a** (Scheme 1, R = Me), the side chain in two of the most populated conformations (**B-a_c1** and **B-a_c3**) is directed toward the α face of the molecule, facilitating the *Si* face hydrogenation that leads to the tricyclic core of 9a-*epi*-stemoamide (**14**). The preference was much more straightforward upon inspection of the hydrogenation of the imine derived from benzyl ester **9b**: the energy differences between the two most stable conformations **B-b_c1** and **B-b_c2** (Fig. 2) were 0.9 kcal mol^{-1} in ethyl acetate and 1.1 kcal mol^{-1} in trifluoroethanol, respectively, with the benzyl group in both conformations directing the hydrogenation from the *Re* face probably due to CH/π interactions,[13] thus leading to the stemoamide core. It should be noted that the computationally obtained energy difference is fully consistent with the 1:10 diastereoisomeric ratio favoring the tricyclic stemoamide core that was observed experimentally in trifluoroethanol at 10 atm of hydrogen pressure. Methylation of lactone **11** to give the natural

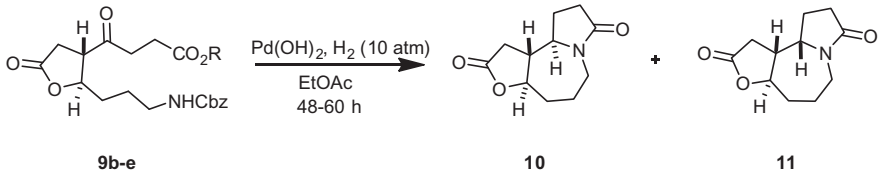


Scheme 2. Preparation of 1,4-dicarbonyl compounds by nitro-Michael and Nef reactions.



Scheme 3. Cascade cyclization reactions. Reagents and conditions: (a) R = Me (**9a**), $Pd(OH)_2/C$ (40% wt/wt), H_2 (2 or 4.5 atm), EtOAc, 48 h, 45%; (b) R = Bn (**9b**), $Pd(OH)_2/C$ (40% wt/wt), H_2 (4.5 atm), EtOAc, 60 h, 42%.

Table 1
Diastereomeric ratio of ring epimers as a function of ester group



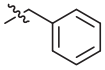
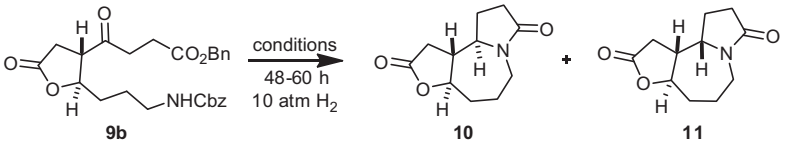
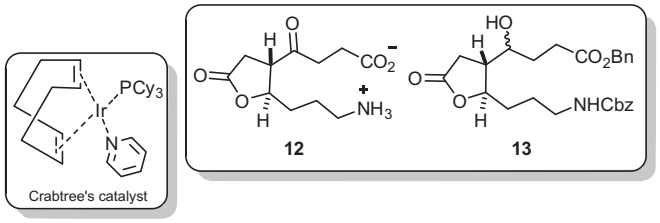
Entry	R	Substrate	Ratio (**10**:**11**)
1		**9b**	1:3
2		**9c**	1:2
3		**9d**	1:1
4		**9e**	3:1

Table 2
Diastereomeric ratio of ring isomers as a function of reaction solvent and catalyst



Entry	Solvent	Catalyst	Ratio (**10**:**11**)
1	EtOAc	$Pd(OH)_2/C$	1:3
2	HOAc	$Pd(OH)_2/C$	1:1.4
3	CF_3CH_2OH	$Pd(OH)_2/C$	1:10[a]
4	EtOAc	PtO_2/C	b
5	EtOAc	Crabtree's	c
6	EtOAc	Ru/C	c

[a] Aminoacid **12** was also isolated.
[b] Only product **13** from carbonyl reduction was observed.
[c] Only starting material was recovered.



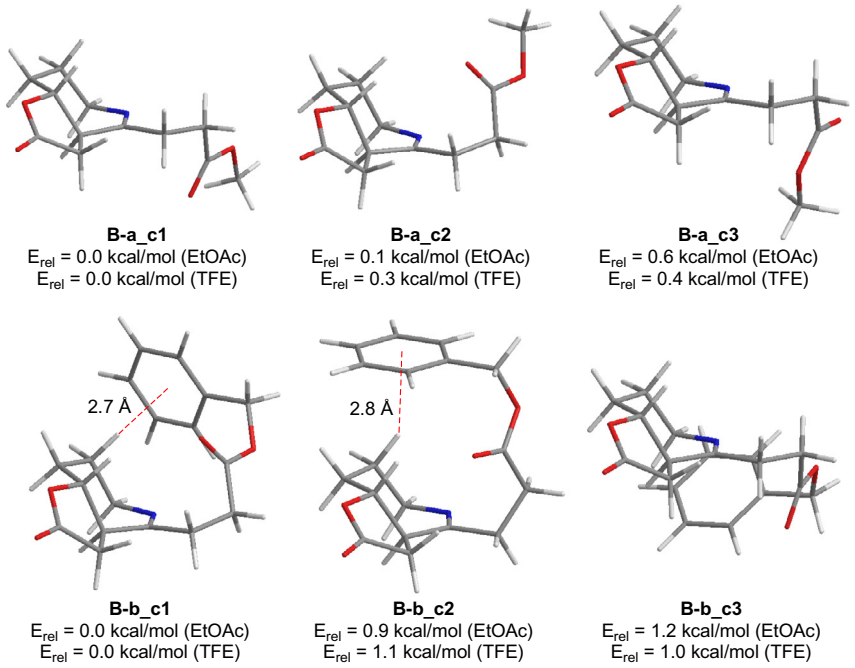
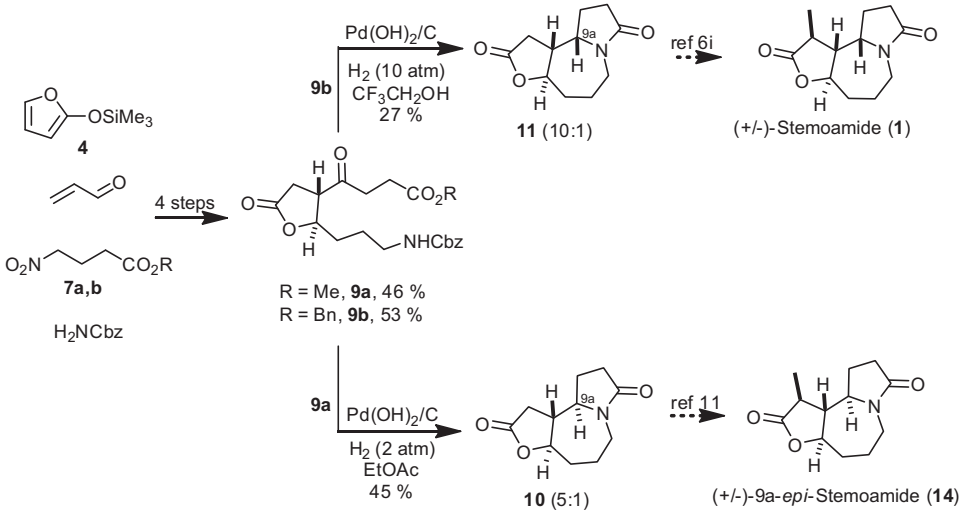


Figure 2. Relative energies of imines derived from esters **9a** and **9b**.



Scheme 4. Overview of the formal total syntheses of epimeric stemoamides.

product **1** has previously been described in the literature (Scheme 4).[6i,11]

In summary, we have developed a reaction sequence that enables a concise formal synthesis of stemoamide (**1**) and its 9a-epimer **14** in 5 steps from commercially available building blocks (Scheme 4). A good selectivity for either epimer is readily accomplished by variation of the ester (**9b** or **9a**, respectively) and the reaction conditions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.017.

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