Natural Products

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Stereoselective Total Syntheses of (−)-Flueggine A and (+)-Virosaine B**

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The identification of new chemical entities is of paramount importance to the biomedical sciences for the development of novel therapeutic agents, and natural products have recently been the subject of renewed and considerable attention in this particular context.[1] *Securinega* alkaloids are an important family of natural products derived from several *Euphorbiaceae* and *Phyllanthus* species of the Euphorbiaceae plant family,[2] and have been used for years in traditional Chinese and the Amazonia folk medicines.[3] More recently, these alkaloids have been reported to exhibit important biological activities, including diuretic, hepatic protection, antimicrobial, antibacterial, and GABAA receptor and tagonism.[4]

One merging class of the *Securinega* alkaloids include (−)-flueggine A (**1**)[5] and (+)-virosaine B (**2**)[6] (Figure 1), which were isolated from the twigs and leaves of *Flueggea virosa* by Ye et al. in 2011 and 2012, respectively. Their structures and absolute configurations were elucidated by means of NMR spectroscopy, single-crystal X-ray diffraction, and circular dichroism (CD) analyses. Other naturally occurring *Securinega* alkaloids include (−)-norsecurinine (**3**),[7] (+)-allonorsecurinine (**4**),[8] securinine (**5**),[7] and flueggine **B** (**6**).[5]

Structurally, both flueggine A (**1**) and (+)-virosaine B (**2**) possess a unique structural framework based on their isoxazolidine and 7-oxa-1-azabicyclo[3.2.1]octane rings, which is unprecedented in the *Securinega* alkaloids. In addition to their unique structural features, **1** exhibited anticancer activities in three cell lines with IC_{50} values of 60 ± 4 μM (MCF-7), 86 ± 9 μM (MDA-MB-231), and 68 ± 7 μM (MCF-7/ADR).[5]

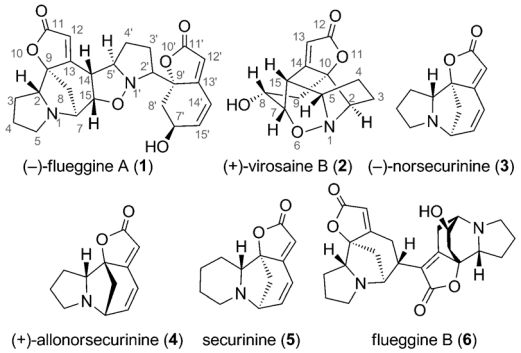

Figure 1. Naturally occurring *Securinega* alkaloids.

In an extension of our continuing efforts toward the total syntheses of biologically active natural products,[9] we decided to synthesize these structurally novel natural products to allow the effective evaluation of their biological properties. Herein, we report the first total syntheses of (−)-flueggine A (**1**) and (+)-virosaine B (**2**) with relay ring-closing metathesis[10] (RRCM) and 1,3-dipolar cycloaddition reactions[11] as the key steps of the approaches.

Retrosynthetically, we envisioned that (−)-flueggine A (**1**) could be generated from (−)-norsecurinine (**3**) and nitrone **7** through a concerted[12] 1,3-dipolar cycloaddition reaction according to the proposed biogenetic pathway (Figure 2).[5] (−)-Norsecurinine (**3**)[13] itself could be generated from the substituted dihydrobenzofuranone **9** by a bromination–substitution sequence. In turn, compound **9** could be generated from enyne **8** through an RRCM reaction. Thus, our strategy for the total synthesis of (−)-flueggine A (**1**) could be traced back to the construction of enyne **8**, which we envisaged could be derived from D-proline (**6**).

Following the biomimetic transformation proposed by Ye and workers,[6] we envisaged that (+)-virosaine B (**2**) could be formed by the intramolecular 1,3-dipolar cycloaddition from nitrone **10**, which could in turn be prepared from (+)-allonorsecurinine (**4**),[8,14] through a process involving a [2,3]-Meisenheimer rearrangement[15] followed by a concerted [1,3]-sigmatropic rearrangement[16] (see also Schemes 4 and 5). It was envisaged that the construction of (+)-allonorsecurinine (**4**) could be achieved from D-proline (**6**) according to a similar process to that descried for the construction of (−)-norsecurinine (**3**) via the key intermediates **11** and **12** (Figure 2).

The key step in our proposed synthesis was the tandem RCM reaction. This reaction represents a powerful synthetic tool and was initially developed by Grubbs et al.[17] in 1994 for the preparation of fused bicyclic ring systems. The reaction

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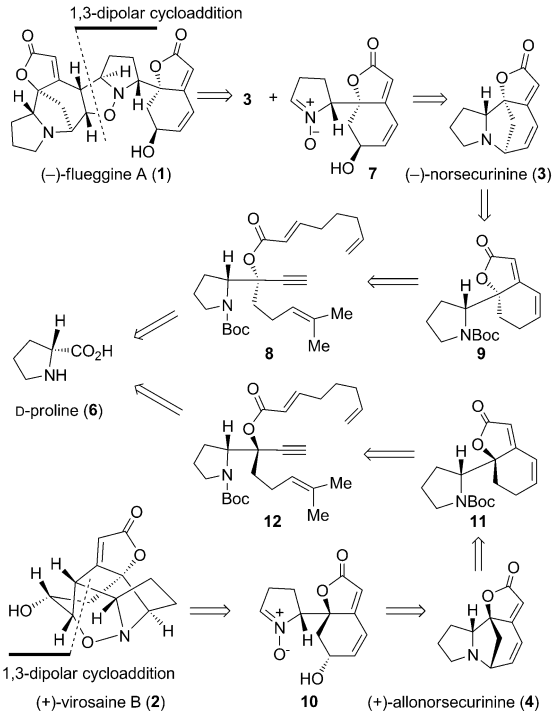
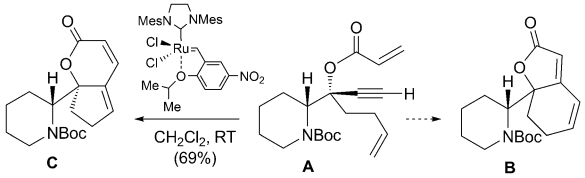


Figure 2. Retrosynthetic analysis. Boc = *tert*-butyloxycarbonyl.

has subsequently been used by many other groups for the construction of a number of complex scaffolds.[18] Encouraged by our recent model study toward the total synthesis of nanolobatolide,[19] we decided to apply this powerful reaction to the construction of (−)-norsecurinine (**3**) and (+)-allonorsecurinine (**4**).

In 2004, Honda et al. attempted to construct the core structure of (−)-securinine through a tandem RCM reaction.[20] Unfortunately, however, the reaction did not provide the desired γ-lactone **B** from **A**, but gave δ-lactone **C** in 69% yield, because the catalyst[21] reacted preferentially with the butenyl group rather than the acrylate moiety[22] to afford the corresponding ruthenium–carbene complex, which undergoes the tandem enyne metathesis (Scheme 1).

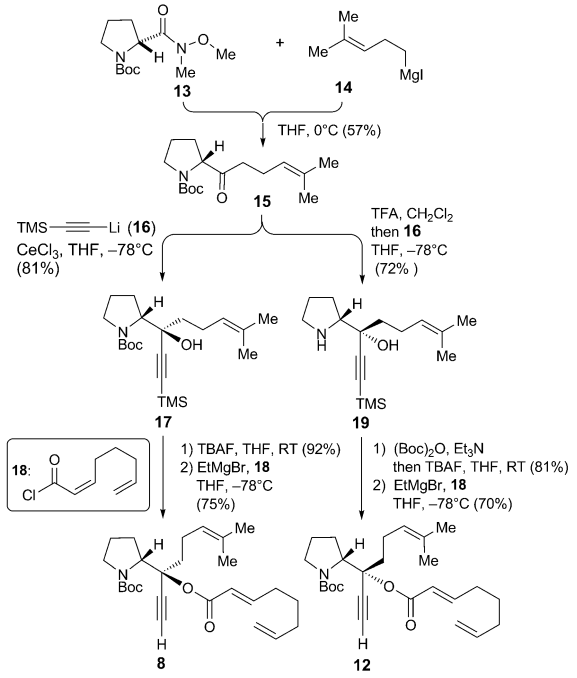
We speculated that the ruthenium-based catalyst would react preferentially with the terminal olefin moieties of substrates **8** and **12** to generate more active ester–carbene complexes,[23] which would initiate the tandem enyne metathesis for the formation of the corresponding annulated products **9** and **11** (Scheme 3). The rationale behind this strategy rests on the fact that the less sterically encumbered terminal olefins in enynes **8** and **12** would react with the ruthenium catalyst first, and then undergo relay metathesis



Scheme 1. Synthesis of δ-lactone **C**. Mes = 2,4,6-trimethylphenyl.

reactions[10a] to generate more active ester–carbene complexes to afford dihydrobenzofuranones **9** and **11**, respectively.

The implementation of our synthetic plan started with the asymmetric syntheses of enynes **8** and **12** (Scheme 2) according to a method originally developed by Honda and co-

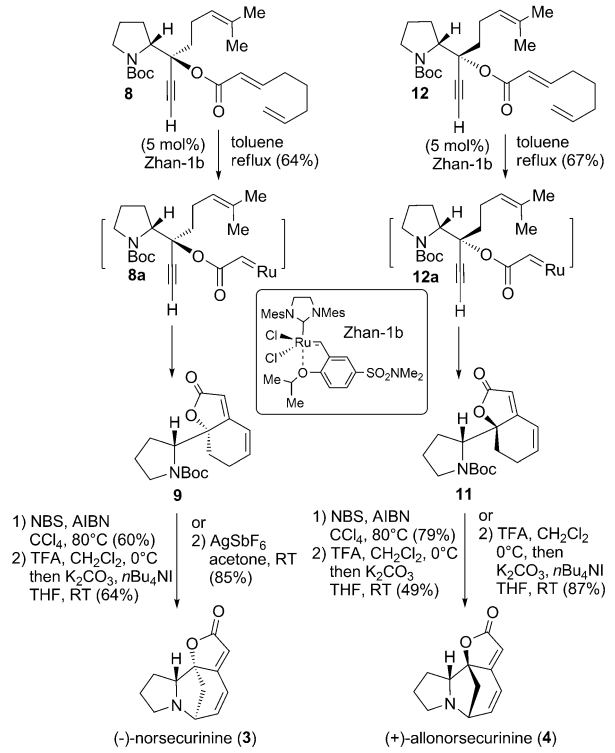


Scheme 2. Syntheses of enynes **8** and **12**. TBAF = tetra-*n*-butylammonium fluoride, TFA = trifluoroacetic acid, TMS = *tert*-butyldimethylsilyl.

workers.[20] First, the commercially available Weinreb amide **13** was reacted with Grignard reagent **14** to give ketone **15** in 57% yield. This material was then treated with lithium trimethylsilylacetylide (**16**) in the presence of $CeCl_3$ to give a tertiary alcohol **17** as the sole product in accordance with the Felkin–Anh model. Subsequent removal of the TMS group in **17** with TBAF followed by acylation of the resulting tertiary alcohol with acryloyl chloride derivative **18** in the presence of EtMgBr as a base in THF at −78 °C gave trienyne **8** in 69% yield over two steps.

For the synthesis of enyne **12**, ketone **15** was treated with TFA to remove its Boc group, and without isolation the resulting secondary amine containing ketone was directly reacted with lithium trimethylsilylacetylide (**16**), affording the chelation-controlled[24] product **19** in 72% yield. Protection of the amine with a Boc group and removal of the TMS group in **19**, followed by acylation of the resulting tertiary alcohol with acryloyl chloride **18**, gave trienyne **12** in 57% yield over two steps.

With enynes **8** and **12** in hand, we proceeded to explore our proposed RRCM reaction for the formation of dihydrobenzofuranones **9** and **11** (Scheme 3). The RRCM reactions of enynes **8** and **12** were tested with several commercially available metathesis catalysts, including Grubbs' second generation, Hoveyda–Grubbs', and Zhan-1b catalysts, with



Scheme 3. Syntheses of (−)-norsecurinine (**3**) and (+)-Allonorsecurinine (**4**). AIBN = azobisisobutyronitrile, NBS = *N*-bromosuccinimide.

the Zhan-1b catalyst providing the best results (see the Supporting Information for further details). Thus, under the optimized conditions, dihydrobenzofuranones **9** and **11** were obtained in 64% and 67% yield, respectively. We infer that the reaction proceeded via the active ester–carbene complexes **8a** and **12a** as key intermediates. To the best of our knowledge, the successful intramolecular reaction of "an active ester–carbene complex" with an alkyne[25] to form an α,β-unsaturated lactone has not been reported to date.

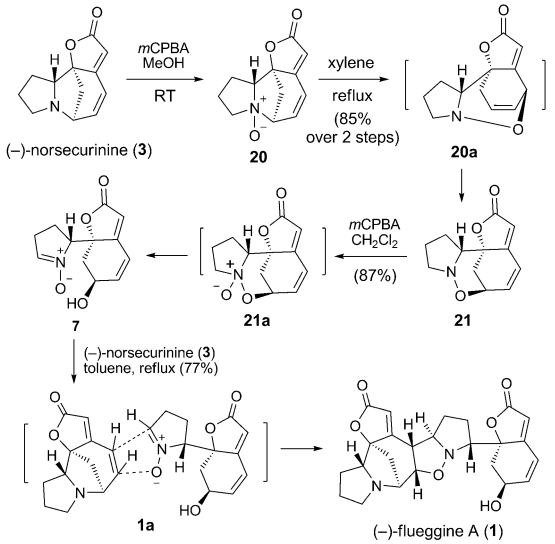
To complete the synthesis of (−)-norsecurinine (**3**), **9** was initially converted to an allylic bromide by treatment with NBS in the presence of AIBN.[20] During our preliminary investigation, a literature procedure[20] was employed to annulate the newly generated allylic bromide, involving the removal of the Boc group with TFA, followed by a K_2CO_3-mediated cyclization, giving (−)-norsecurinine (**3**) in 64% yield. We later discovered that the bromide could be directly annulated under the optimized conditions in the presence of $AgSbF_6$ in acetone to give (−)-norsecurinine (**3**) in 85% yield. In this reaction, $AgSbF_6$ might play the roles of both the Lewis acid to deprotect the Boc group in the presence of trace amounts of water,[26] and the Ag^+ ion that captures the newly formed bromide ion, thus making the latter a better leaving group. The physical properties of the synthetic (−)-norsecurinine (**3**) were compared to those reported for the natural product and found to be in good agreement,[7] including the ^1H and ^{13}C NMR data and the optical rotation.

In a similar fashion, **11** was converted to the corresponding bromide in 79% yield with NBS and AIBN. Unfortunately, however, when the bromide was treated with $AgSbF_6$ in acetone, the desired (+)-allonorsecurinine (**4**) was not obtained. In contrast, (+)-allonorsecurinine (**4**) was formed in 49% yield when **11** was initially deprotected with TFA, followed by annulation with K_2CO_3 in THF.

Interestingly, when the latter reaction was carried out in the presence of nBu_4NI, the yield for the formation of (+)-allonorsecurinine (**4**) was improved to 87%, presumably as a consequence of a bromo–iodo exchange reaction. The physical properties of synthetic **4** were in good agreement with those reported for the natural material.[8]

With (−)-norsecurinine (**3**) and (+)-allonorsecurinine (**4**) in hand, we proceeded toward our proposed total syntheses of (−)-flueggine A (**1**) and (+)-virosaine B (**2**).

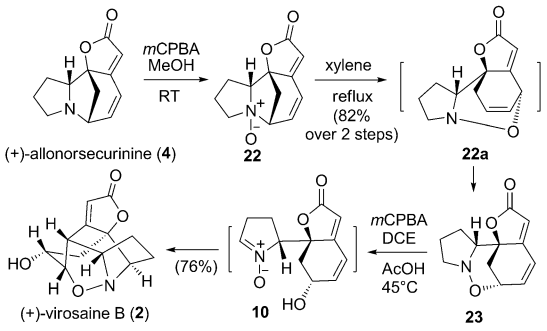
Following the protocol developed by Magnus et al.,[27] (−)-norsecurinine (**3**) was treated with *m*CPBA in MeOH to chemoselectively afford *N*-oxide **20** (Scheme 4). The *N*-oxide was then heated to reflux in xylene to initiate the



Scheme 4. Total Synthesis of (−)-flueggine A (**1**). *m*CPBA = *meta*-chloroperoxybenzoic acid.

sequential [2,3]-Meisenheimer and [1,3]-sigmatropic rearrangements to afford *O*-alkylhydroxylamine **21** in 90% yield via intermediate **20a**. Further treatment of **21** with *m*CPBA[27,28] gave nitrone **7** via **21a**. Compound **7** was then reacted with (−)-norsecurinine (**3**) in refluxing toluene for 12 h to afford (−)-flueggine A (**1**) through a 1,3-dipolar addition in 77% yield. The ^1H and ^{13}C NMR spectra of the synthesized (−)-flueggine A (**1**) were identical to those reported for the natural product. The optical rotation was also in good agreement (synthetic **1**: $[\alpha]_D^{30} = -32.8$ ($c = 0.20$, CH_3OH); natural **1**: $[\alpha]_D^{20} = -31.9$ ($c = 0.25$, CH_3OH)).

For the total synthesis of (+)-virosaine B (**2**), (+)-allonorsecurinine (**4**) was chemoselectively oxidized to its corresponding *N*-oxide **22** in 98% yield (Scheme 5). The *N*-oxide was then heated to reflux in toluene to afford *O*-alkylhydroxylamine **23** in 84% yield. During our initial investigation, the intramolecular 1,3-dipolar cycloaddition reaction of nitrone **10**, which was readily formed by further oxidation of **23** with



Scheme 5. Synthesis of (+)-virosaine B (**2**). DCE = 1,2-dichloroethane.

*m*CPBA in DCE, furnished (+)-virosaine B (**2**) in 46% yield. Interestingly, however, when the reaction was carried out in the presence of AcOH, the yield of the desired product (+)-virosaine B (**2**) was further improved to 76%. The spectroscopic data of the synthesized (+)-virosaine B were consistent with those reported for the natural product.[6] The optical rotation of the synthetic sample was also in good agreement with that of the natural product (synthetic **2**: $[\alpha]_D^{30} = = +65.7$ ($c = 0.70$, CH_3OH), natural **2**: $[\alpha]_D^{20} = +62.7$ ($c = 0.50$, CH_3OH)).

In summary, concise and asymmetric syntheses of (−)-flueggine A (**1**) and (+)-virosaine B (**2**) have been achieved for the first time through biomimetic approaches[5] starting from the commercially available Weinreb amide **13**, and the absolute configurations of these natural products have been established. The total syntheses of **1** and **2** proceed in 11 and 10 steps with 5.92% and 6.68% overall yield, respectively, with tandem RRCMs and 1,3-dipolar cycloadditions as the key steps. This novel synthetic strategy for the formation of dihydrobenzofuranones could be used as a general method for organic synthesis.

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