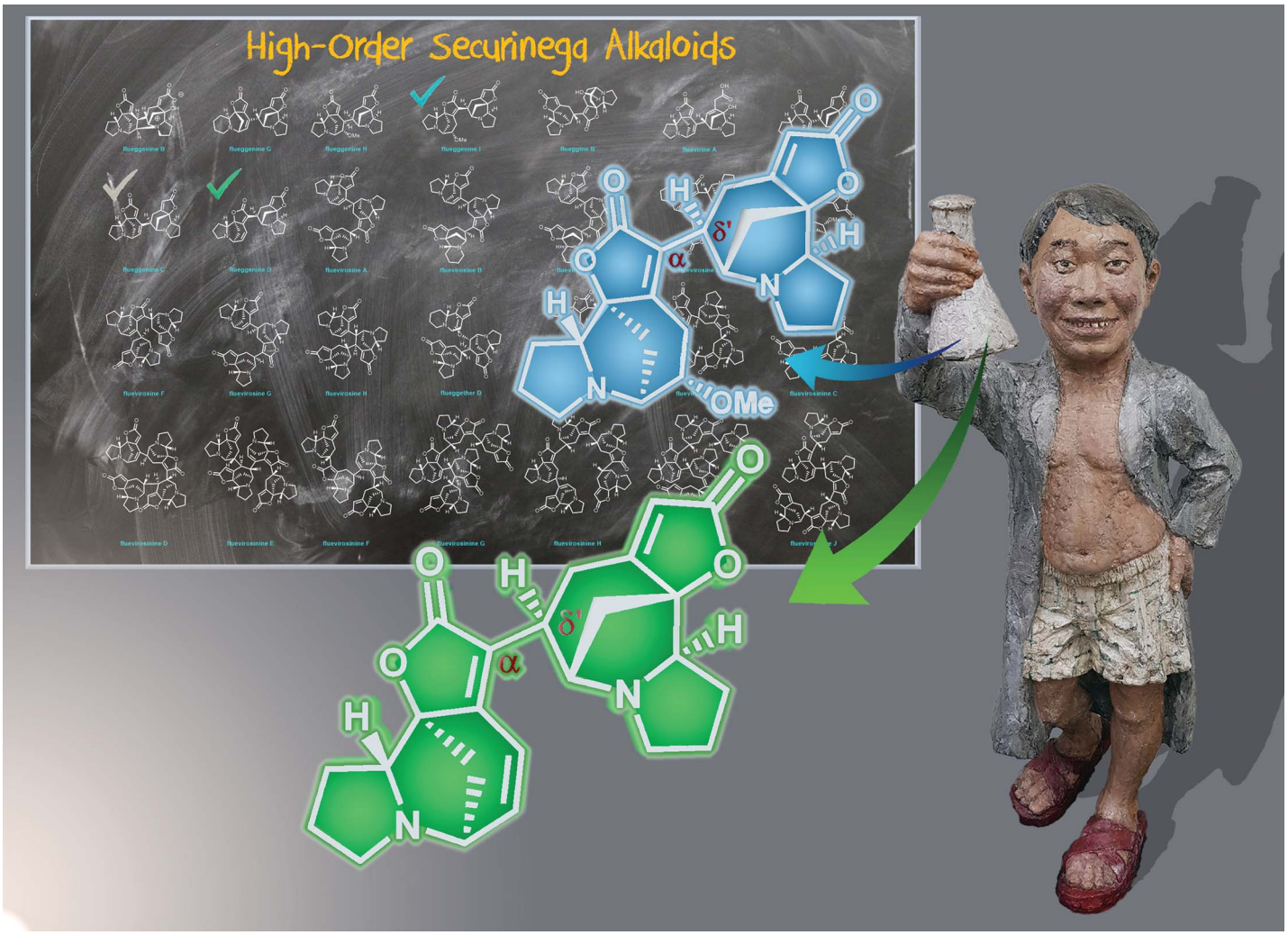
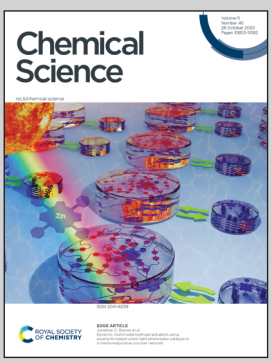


Showcasing research from Professor Sunkyu Han's laboratory, Department of Chemistry, Korea Advanced Institute of Science and Technology, Republic of Korea.

Total synthesis of dimeric *Securinega* alkaloids (−)-flueggenines D and I

Presented here is the total synthesis of (−)-flueggenines D and I. This features the first total synthesis of dimeric *Securinega* alkaloids with a C(α)–C(δ′) connectivity between two monomeric units. The key dimerization was enabled by a sequence that involves Stille reaction and conjugate reduction. Stereochemical flexibility and controllability at the δ′-junction of the dimeric intermediate render our synthetic strategy broadly applicable to the synthesis of other high-order *Securinega* alkaloids. The statue in the image was produced by Professor Changkyu Han in the Dept. of Formative Art Contents at Mokwon University.

As featured in:



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Total synthesis of dimeric *Securinega* alkaloids (−)-flueggenines D and I†

Sangbin Jeon, Jinwoo Lee, Sangbin Park and Sunkyu Han *

We describe the total synthesis of (−)-flueggenines D and I. This features the first total synthesis of dimeric *Securinega* alkaloids with a C(α)–C(δ′) connectivity between two monomeric units. The key dimerization was enabled by a sequence that involves Stille reaction and conjugate reduction. The high chemofidelity of the Stille reaction enabled us to assemble two structurally complex fragments that could not be connected by other methods. Stereochemical flexibility and controllability at the δ′-junction of the dimeric intermediate render our synthetic strategy broadly applicable to the synthesis of other high-order *Securinega* alkaloids.

Introduction

Securinega alkaloids isolated from plants of the genera *Flueggea*, *Securinega*, *Phyllanthus*, *Brenia* and *Margaritaria* have fascinated the chemical community for over six decades.[1] Despite numerous structural variations, a typical monomeric *Securinega* alkaloid consists of a tetracyclic framework (A–D rings) that is decorated with α,β–γ,δ-unsaturated ester and tertiary amine moieties (Fig. 1). This unique molecular architecture is responsible for numerous biological activities and has served as an inspiration for over 30 total syntheses.[2] A breakthrough in *Securinega* natural products chemistry was recorded in 2006 when Yue and coworkers isolated the first dimeric *Securinega* alkaloids flueggenines A (**2**) and B from *Flueggea virosa*.[3] Since this initial report, continued isolation campaigns of this family of secondary metabolites have resulted in discoveries of 38 dimeric and oligomeric (high-order) *Securinega* natural products to date.[1,4]

A closer structural examination of all known high-order *Securinega* alkaloids reveals that 28 of them (74%) are biosynthesized by a presumed enzymatic Rauhut–Currier (RC) reaction, a reaction that involves a carbon–carbon bond formation between two Michael acceptors.[5,6] Flueggenine A (**2**) consists of two norsecurinine (**1**) units that are connected by an RC reaction-based C(γ)–C(δ′) bond (Fig. 1, highlighted in yellow).[3] Flueggenine C (**3**) retains the atoms connectivity of flueggenine A (**2**) but exhibits opposite configuration at the δ′ junction implying the importance of stereochemical flexibility and controllability at this site when approaching this family of natural products by chemical synthesis.[7]

Another mode of connectivity within high-order *Securinega* alkaloids is the C(α)–C(δ′) connection (Fig. 1, highlighted in cyan) exemplified by anti-HIV agent flueggenine D (**4**)[7] and its methoxy adduct flueggenine I (**5**).[8] In addition to dimers, several trimeric *Securinega* alkaloids such as fluevirosine B (**6**)[9] have also been isolated. It is important to note that connections

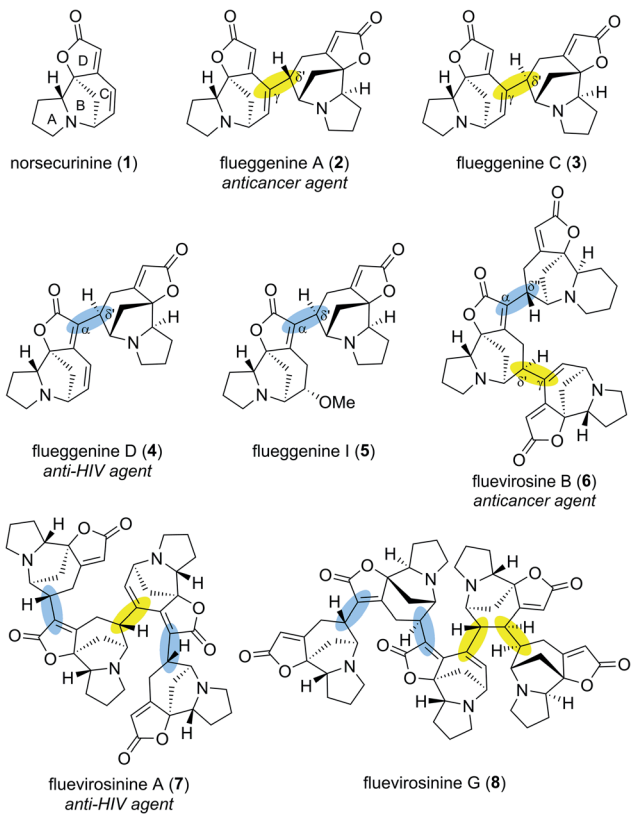

Fig. 1 Norsecurinine (**1**) and representative high-order *Securinega* alkaloids.

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† Electronic supplementary information (ESI) available: Comprehensive experimental procedures, spectroscopic data, spectrometric data, and copies of ^{1}H, ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/d0sc03057k

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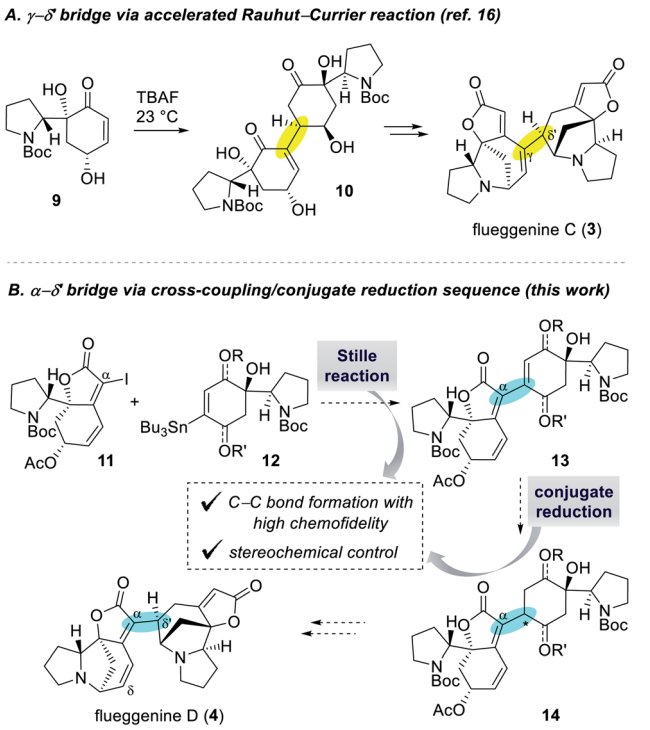
between monomeric units within these trimers involve either C(γ)–C(δ′) or C(α)–C(δ′) bonds. Notably, these γ–δ′ and α–δ′ connections are the sole bonds that constitute the covalent networks of even higher-order *Securinega* natural products such as tetrameric fluevirosinine A (**7**)[7] and pentameric fluevirosinine G (**8**).[10] Hence, development of strategies that enables the C(γ)–C(δ′) and C(α)–C(δ′) bonds formation between *Securinega* monomers with stereochemical control is essential in synthesizing 28 known RC-based high-order *Securinega* alkaloids.

Despite numerous examples of monomeric *Securinega* alkaloids syntheses,[1,11] there have been only a few examples of synthesis of dimeric *Securinega* natural products.[12–15] Especially, synthetic access to RC reaction-based dimeric *Securinega* alkaloids had remained an unsolved problem until our recent total synthesis of (−)-flueggenine C (**3**) by an accelerated RC reaction (Scheme 1A).[16] We showed that γ-hydroxy enone derivative **9** undergoes an efficient and stereoselective RC reaction to yield dimer **10**. This compound could be moved forward to (−)-flueggenine C (**3**) with the γ–δ′ connectivity. While optimal for the synthesis of flueggenine C (**3**), the accelerated RC reaction could not be applied to the synthesis of its δ′-epimer, flueggenine A (**2**).[17] Moreover, we could not expand this strategy into the formation of the C(α)–C(δ′) bond. Hence, we embarked on the development of a new dimerization strategy that overcomes these limitations and set (−)-flueggenine D (**4**) as our primary synthetic target.

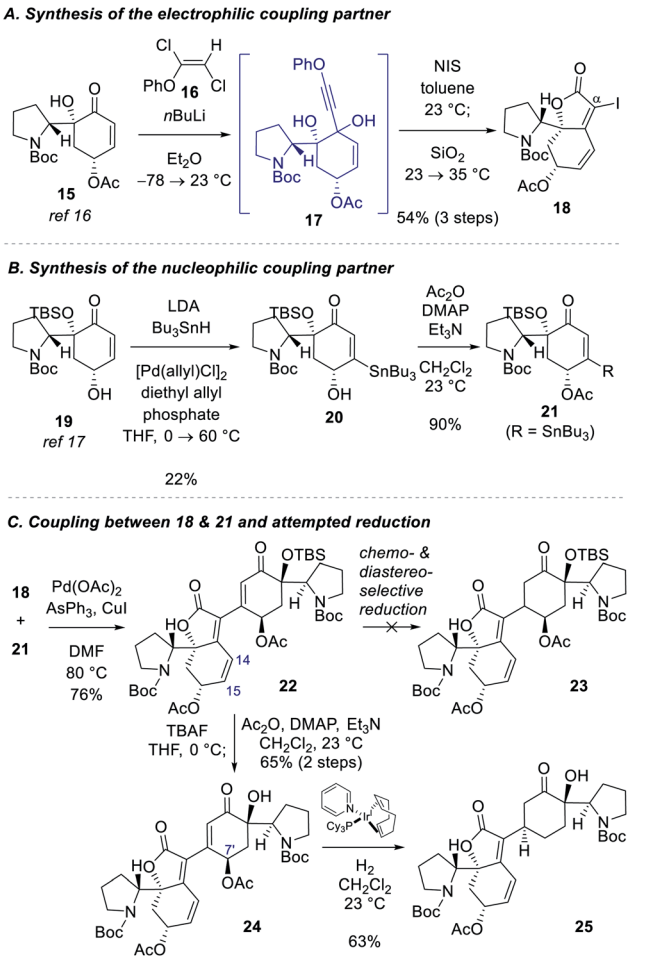
Extensive preliminary studies aimed at the C(α)–C(δ′) bond formation involving metal catalyzed conjugate additions, (reductive) Heck reactions, and radical-based approaches turned unfruitful. At this juncture, we envisioned to utilize Stille cross-coupling reaction for the key C(α)–C(δ′) bond formation due to its proven high chemofidelity[18] in complex molecular settings (Scheme 1B).[19] We planned to couple iodide **11** and organostannane **12** *via* a Stille reaction to obtain dimeric precursor **13**. Conjugate reduction of enone derivative **13** would yield compound **14** with controllable configuration at the connection junction. Precursor **14** with the desired C(α)–C(δ′) bond connectivity and stereochemistry was projected to be transformed to (−)-flueggenine D (**4**) and its C(δ)-methoxy adduct (−)-flueggenine I (**5**).



Scheme 1 Dimerization strategies for the synthesis of high-order *Securinega* alkaloids.

Results and discussion

Our studies commenced with the synthesis of the electrophilic coupling partner for Stille cross-coupling reaction (Scheme 2A). Our previously accessed enone **15** (8 steps from *N*-Boc-D-proline)[16] was allowed to react with lithium phenylacetylide generated *in situ* from phenoxy dichloroethene **16** to produce propargyl alcohol intermediate **17**.[20] Treatment of **17** with NIS followed by stirring of the reaction mixture with silica gel provided α-iodobutenolide **18** in 54% yield over 3 steps. A plausible reaction mechanism for the transformation of **17** to **18** might involve an iodo Meyer–Schuster rearrangement[21] but we cannot rule out a direct iodine-induced 5-*endo*-dig cyclization.[22]



Scheme 2 Initial synthetic approach toward (−)-flueggenine D (**4**).

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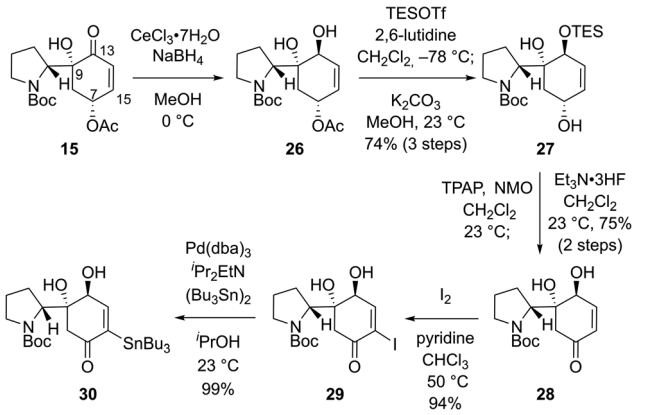


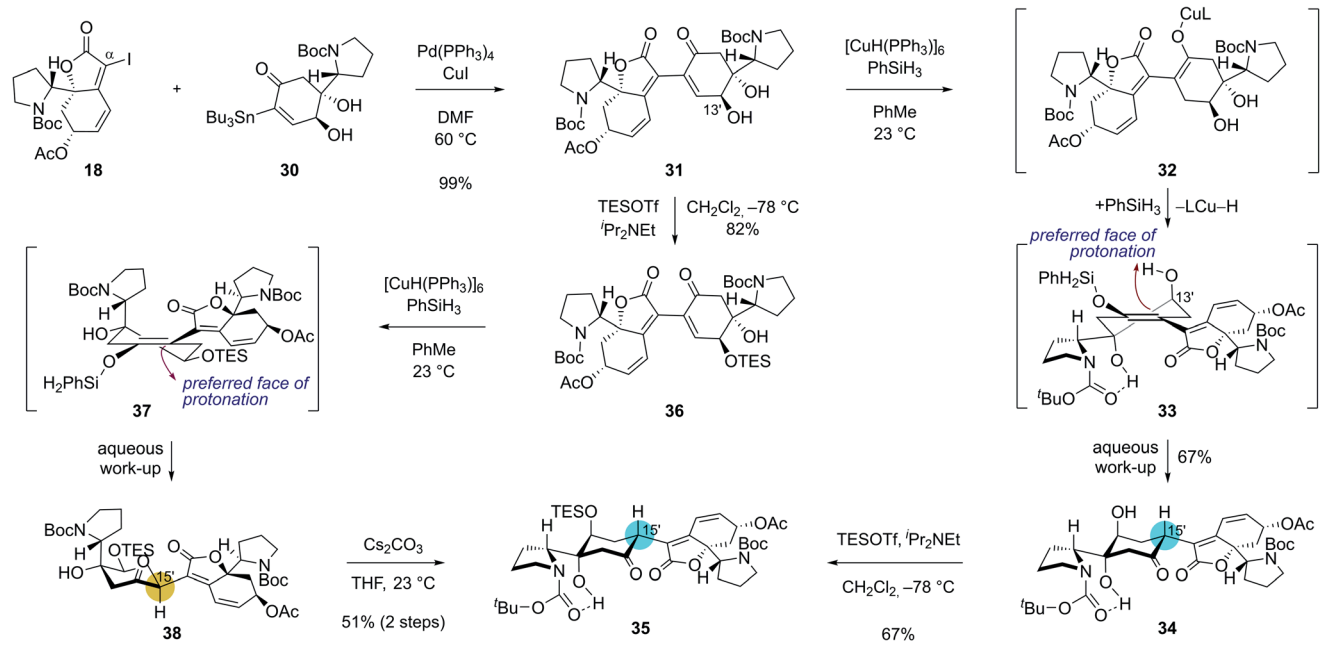
Scheme 3 Re-design of the organostannane coupling partner.

For the synthesis of the nucleophilic coupling partner of the Stille reaction, we invoked a Pd-catalyzed oxidative β-stannylation of enone that was recently reported by the Newhouse group (Scheme 2B).[23] We found that our previously reported enone **19**[17] delivered stannane **20** in 22% yield under Newhouse's conditions. The hydroxyl group of **20** was subsequently acylated to yield stannane **21** in 90% yield. With both coupling partners **18** and **21** available, we attempted the Stille cross-coupling reaction between them. In the presence of $Pd(OAc)_2$, triphenylarsine, and CuI, iodide **18** and stannane **21** were coupled to yield enone **22** in 76% yield (Scheme 2C).

However, the chemoselective conjugate reduction of **22** to **23** turned problematic. We could not obtain any desired product under various conjugate reduction or Pd-catalyzed hydrogenation conditions. We only observed the reduction at the C14–C15 double bond of the unsaturated ester moiety in the left fragment under these conditions. Attempted hydroxyl-directed hydrogenation of cyclohexenone **24** derived from **22** in 65% yield over 2 steps using Crabtree's catalyst[24] resulted in allylic deacetoxylation at the C7′ position followed by a stereoselective hydrogenation of the enone group to provide saturated ketone **25** in 63% yield. Modest yield of the β-stannylation of enone **19** and unsuccessful conjugate reduction of the β-substituted cyclohexenones **22** and **24** necessitated us to modify the synthetic approach.

We envisioned that problems encountered in our initial synthetic route (Scheme 2B and C) can be solved by introducing a ketone group at the C7 position of bicyclic compound **15** (Scheme 3). Firstly, it would make the introduction of the stannyl group at C15 (flueggenine D numbering) easier because there are more reported methods for the α-functionalization of enone than its β-functionalization. Secondly, the substrate for a conjugate reduction post-Stille reaction would be a "β-unsubstituted" cyclohexenone derivative which has more successful precedences compared to the β-substituted cyclohexenone derivative. Thirdly, after the dimerization and conjugate reduction, the ketone group juxtaposed to the C15′ methine can provide stereochemical flexibility at this junction due to possible deprotonation.

Based on these rationales, ketone **15** was diastereoselectively reduced to diol **26** under Luche's conditions (Scheme 3). Notably, deacetylation and oxidation at C7 of **15** caused immediate dehydration and quinone derivative formation. Silylation of the allylic alcohol moiety in **26** followed by methanolysis of the acetyl group yielded allylic alcohol **27** in 74% yield over 3 steps. Ley oxidation of allylic alcohol **27** and subsequent desilylation produced enone **28** in 75% yield over 2 steps. As expected, α-functionalization of enone **28** was facile. α-Iodination of enone **28** (94% yield) and consequent Pd-catalyzed



Scheme 4 Key dimerization sequence with complete stereochemical flexibility and controllability at the C15′ connection junction.

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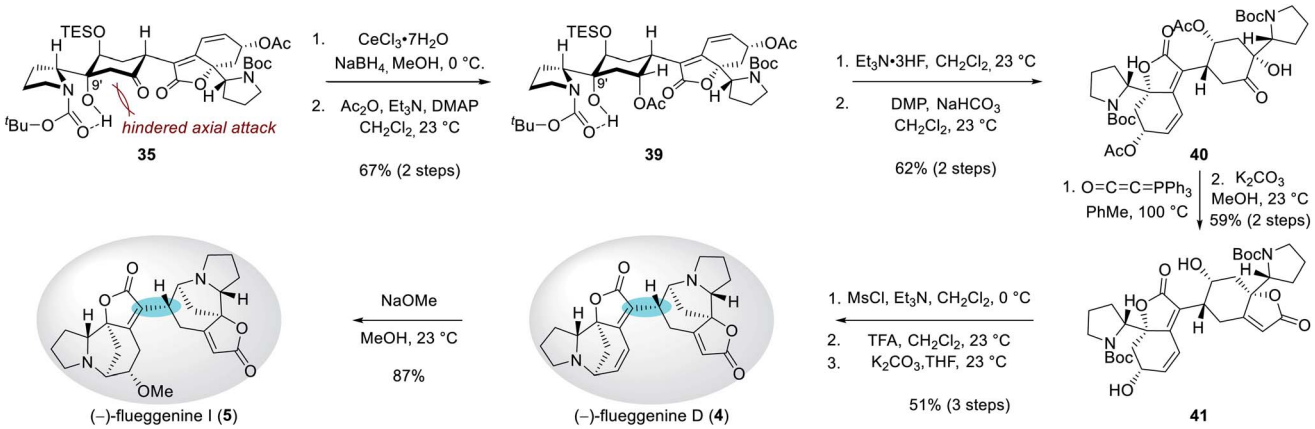

Scheme 5 Total synthesis of (−)-flueggenines D (**4**) and I (**5**).

stannylation using bis(tributyltin) (99% yield) afforded stannane **30** in a reliable manner.

With robust synthetic accesses to both **18** and **30**, we allowed them to react in the presence of catalytic $Pd(PPh_3)_4$ (20 mol%) and CuI additive. Coupled product **31** was obtained in 99% yield (Scheme 4) under these conditions highlighting the robustness of Stille reaction in a complex molecular setting. We next set out for the conjugate reduction of the enone moiety in **31**. Delightfully, treatment of enone **31** with 0.3 equiv. of Stryker's reagent and 5.0 equiv. of phenylsilane afforded conjugatively reduced ketone **34** in 67% yield along with <5% of its C15′ epimer.[25] The lower energy of chair-conformation transition state with minimal torsional strains resulting from the protonation of silyl enol ether intermediate **33** from the top face might have contributed to the observed diastereoselectivity. Intramolecular proton delivery from the C13′ hydroxyl group during the protonation of silyl enol ether intermediate **33** might have also contributed to the observed high diastereoselectivity. Silylation of the secondary alcohol moiety in **34** required for the later chemodifferentiation was achieved in 67% yield.

Interestingly, the stereochemical outcome of the Stryker's reagent-catalyzed conjugate reduction could be reversed when silyl ether **36** that is derived from alcohol **31** upon silylation at C13′ hydroxyl group was utilized as a substrate (Scheme 4). When **36** was treated with Stryker's reagent and phenylsilane for the conjugate reduction, saturated ketone **38** with an *S*-configuration at C15′ was obtained as a single diastereomer. The high diastereoselectivity during the protonation of the silyl enol ether intermediate **37** is reasoned to stem from its preferential protonation from the bottom face that leads to a chair conformation transition state with minimized torsional strains. Importantly, ketone **38** underwent complete epimerization at the C15′ position upon treatment with cesium carbonate in THF to yield the thermodynamic product **35** (51% yield over 2 steps). These observations highlight the stereochemical flexibility and controllability of our synthetic strategy at the pivotal δ′ connection junction.

Reduction of the C7′ ketone group of **35** under Luche's conditions followed by acetylation of the resulting secondary alcohol produced compound **39** in 67% yield over 2 steps (Scheme 5). The observed equatorial attack of the hydride during the reduction step can be rationalized by a hindered axial Bürgi–Dunitz trajectory by the C9′ hydroxyl group. Desilylation of **39** and subsequent Dess–Martin periodinane-mediated oxidation of the resulting alcohol afforded ketone **40** in 62% yield over 2 steps. For the construction of the butenolide moiety, hydroxyketone **40** was treated with Bestmann ylide at 100 °C in toluene.[26] Subsequent methanolysis produced diol **41** in 59% yield over 2 steps. Parallel mesylations of both alcohol groups in **41**, Boc deprotections, and subsequent *N*-alkylations under basic conditions resulted in the first synthetic sample of (−)-flueggenine D (**4**) in 51% yield over 3 steps. NMR, HRMS, and specific rotation data of our synthetic sample were in agreement with the reported data from the isolation paper.[7] Finally, (−)-flueggenine D (**4**) could be converted to (−)-flueggenine I (**5**) upon its treatment with sodium methoxide in methanol solution in 87% yield enabling its first total synthesis as well. The complete stereoselectivity during this 1,6-conjugate addition reaction is notable.[27]

Conclusions

In conclusion, we have completed the first total synthesis of dimeric *Securinega* alkaloids (−)-flueggenines D (**4**) and I (**5**) *via* a Stille reaction/conjugate reduction-based dimerization strategy. This constitutes the first synthetic entry to dimeric *Securinega* alkaloids with the C(α)–C(δ′) connectivity between monomeric units. The high chemofidelity of the Stille reaction enabled us to link two structurally complex coupling partners that could not be connected by other methods. Our synthetic strategy features stereochemical flexibility and controllability at the α–δ′ connection junction that are indispensable in accessing other RC reaction-based high-order *Securinega* alkaloids. With chemical technologies to make both α–δ′ (this study) and γ–δ′[16] connections, we can now envision to synthesize trimer or even higher-order *Securinega* natural products that contain both connection modes. Those will be the subjects of our forthcoming reports.

Conflicts of interest

There are no conflicts to declare.

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