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Total synthesis of (−)-flueggenine A and (−)-15′-*epi*-flueggenine D†

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Securinega alkaloids, known for their unique structures and neuroplasticity-inducing potential, are promising candidates for treating neurodegenerative diseases such as depression and substance use disorders (SUD). Herein, we delineate the total synthesis of two dimeric Rauhut–Currier (RC) reaction-based securinega alkaloids, (−)-flueggenine A and (−)-15′-*epi*-flueggenine D. The key step involved a novel reductive Heck dimerization strategy, utilizing a silyl-tethered enone coupling partner to ensure the desired reactivity and stereoselectivity. This dimerization method, combined with established chemistry explored en route to (−)-flueggenines C and D, offers a comprehensive synthetic approach for accessing all known RC-based oligomeric securinega alkaloids.

Introduction

Securinega alkaloids have fascinated the synthetic community for over 60 years due to their unique molecular architectures[1] and potent biological activities.[2] The tetracyclic monomeric (nor)securinane framework characterized by the butenolide moiety and the tertiary amine group has spurred the development of novel synthetic strategies and tactics.[3,4] Recently, it has been reported that securinega alkaloids can act as neuroplastogens,[5–7] rendering them promising candidates for the development of therapeutics against neurodegenerative diseases such as depression and SUD.[8,9]

Organisms have evolved to synthesize diverse natural products from a common precursor, optimizing the production of secondary metabolites and thereby gaining selective advantages. To expand the structural repertoires of secondary metabolites, organisms often biosynthesize oligomeric natural products by conjugating a well-defined monomeric unit.[10] The plant *Flueggea virosa* has also adopted this strategy by biosynthesizing various RC reaction-based oligomeric securinega alkaloids such as fluevirosines A (**1**, Fig. 1),[11] D (**2**),[12] and G (**3**),[13] and fluevirosinines F (**4**) and H (**5**).[14]

Notably, the monomeric norsecurinine units that consist of these oligomeric securinega alkaloids are conjugated by four different types of connectivity that are exemplified in dimeric securinega alkaloid flueggenines A (**6**),[15] C (**8**), and D (**9**),[12] and 15′-*epi*-flueggenine D (**7**). For example, the C(14)–C(15′) bond with an (*R*)-configuration at C15′ present in flueggenine A (**6**, type A connection) and the C(12)–C(15′) bond with an (*S*)-configuration at C15′ present in flueggenine D (**9**, type D connection) are two connection types that conjugate three

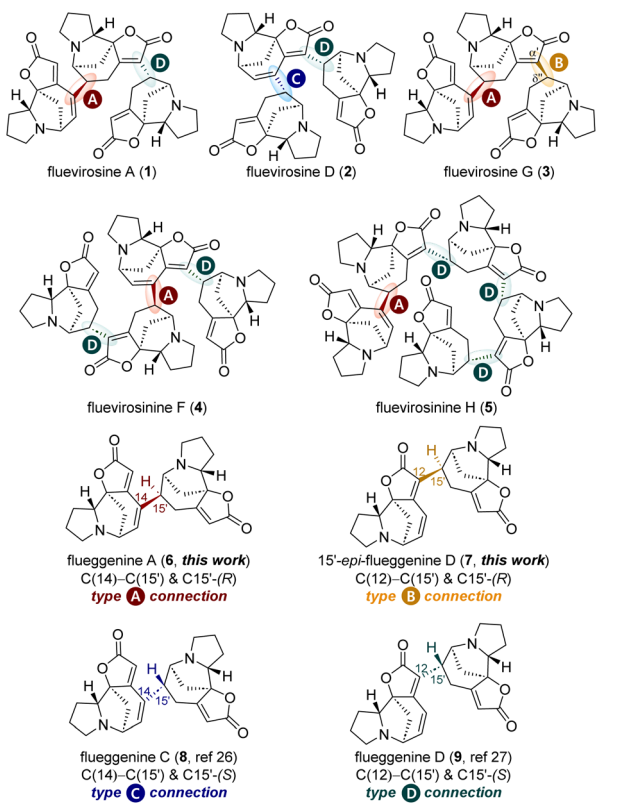

Fig. 1 Representative Rauhut–Currier reaction-based high-order securinega alkaloids.

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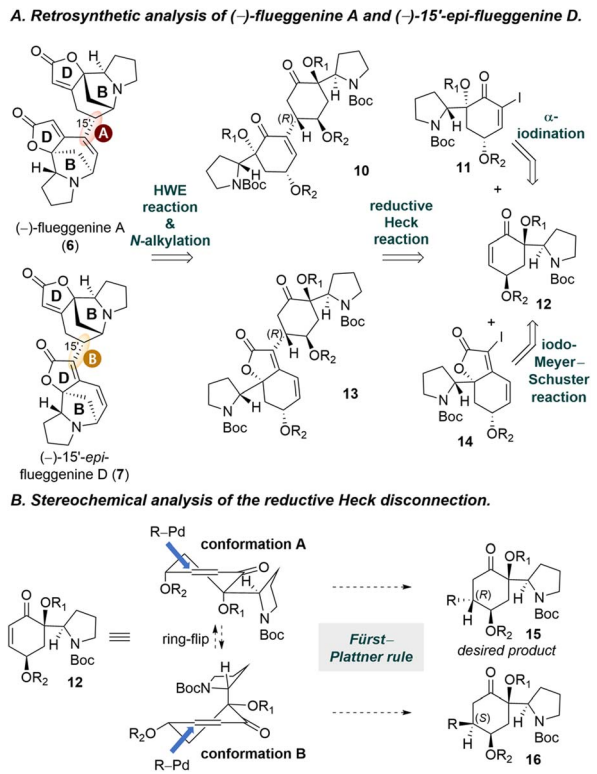
norsecurinine units in fluevirosine A (**1**). Similarly, norsecurinines that consist of trimeric fluevirosine D (**2**) are conjugated by types C and D connections found in dimeric flueggenines C (**8**) and D (**9**), respectively (Fig. 1). It is notable that fluevirosine G (**3**) is networked by type A connection and the connection that conjugates the C(α′) and C(δ″) positions with an (*R*)-configuration at the C(δ″) site. The latter connection (type B) is present in 15′-*epi*-flueggenine D (**7**), a presumed natural product yet to be discovered.[16,17] An analysis of all RC-based high-order securinega alkaloids has shown that these four types of connections encompass all the conjugations among monomers found in this family of natural products.

Despite significant advancement in the total synthesis of monomeric securinega alkaloids,[3,4] the synthesis of dimeric securinega alkaloids has been more challenging with fewer successful cases.[18–23] Our group has been interested in the total synthesis of RC-based high-order securinega alkaloids.[24,25] In 2017, we reported the total synthesis of (−)-flueggenine C (**8**) *via* an accelerated RC reaction strategy.[26] In 2020, our group described the total synthesis of flueggenine D (**9**) enabled by a dimerization strategy involving a Stille cross-coupling reaction and a stereoselective conjugate reduction.[27] However, these dimerization strategies could not be applied to the synthesis of flueggenine A (**6**) or the 15′-epimer of flueggenine D, the missing pieces needed to complete the conjugation network of RC-based oligomeric securinega alkaloids.[28] Herein, we describe a new dimerization strategy that enables types A and B connections for the total synthesis of (−)-flueggenine A (**6**) and (−)-15′-*epi*-flueggenine D (**7**).

Results and discussion

Retrosynthetic analysis of (−)-flueggenine A (**6**) and (−)-15′-*epi*-flueggenine D (**7**) is presented in Scheme 1A. We envisioned to assemble the B-rings present in flueggenine A (**6**) and 15′-*epi*-flueggenine D (**7**) *via* parallel intramolecular *N*-alkylation reactions. For the construction of the butenolide D-rings, intramolecular Horner–Wadsworth–Emmons (HWE) reactions would be employed. We planned to apply a reductive Heck reaction for the key dimerization. While flueggenine A precursor **10** would be derived from a reductive Heck reaction between alkenyl iodide **11** and enone **12**, *epi*-flueggenine D precursor **13** was designed to be accessed from a reductive Heck reaction between iodide **14** and the common enone **12**. Iodides **11** and **14** were planned to be accessed from common enone **12** *via* an α-iodination reaction and an iodo-Meyer–Schuster reaction, respectively.

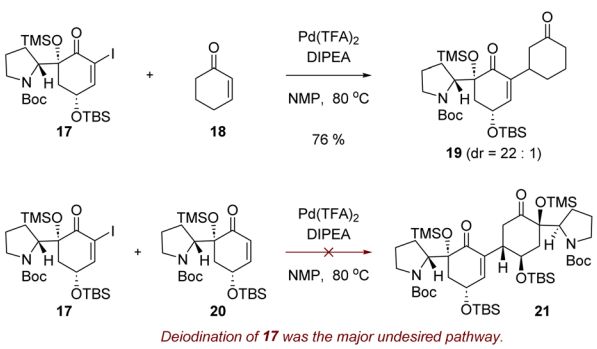
We predicted that the stereochemical outcome of the reductive Heck reaction would be influenced by the conformation of enone **12**. Enone **12** would adopt either conformation A or B (Scheme 1B). According to the Fürst–Plattner rule,[29] when compound **12** assumes conformation A, the alkenylpalladium species approaches from the top face to avoid an unfavorable twist boat-like transition state, resulting in product **15** with the desired (*R*)-configuration at the connection junction. On the other hand, in conformation B, the alkenylpalladium intermediate would approach from the bottom face to yield compound



Scheme 1 Synthetic design of (−)-flueggenine A (**6**) and (−)-15′-*epi*-flueggenine D (**7**).

16 with an (*S*)-configuration at the connecting carbon. For the latter case, we anticipated that the protected allylic hydroxyl moiety may hinder the approach of the organopalladium species. Taking into consideration the sterically bulky nature of the Boc-protected pyrrolidine moiety, we initially anticipated that conformation A of enone **12** would be favored over conformation B.

To test the plausibility of the reductive Heck dimerization strategy, we initially attempted the reaction with alkenyl iodide **17** and cyclohexenone (**18**). Pleasantly, when iodide **17** and cyclohexenone (**18**) were heated in the presence of 5 mol% of palladium(II) trifluoroacetate ($Pd(TFA)_2$) and diisopropylethylamine (DIPEA) in *N*-methyl-2-pyrrolidone (NMP),[30] reductive Heck reaction product **19** was obtained in 76% yield as a 22 : 1 mixture of diastereomers (Scheme 2). Encouraged by these

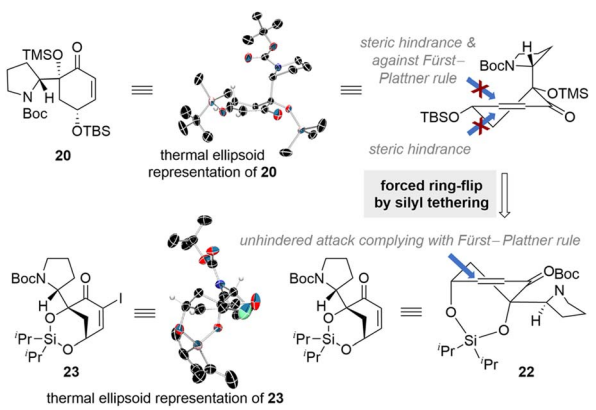


Scheme 2 Initial attempts for the reductive Heck reaction.

results, we next attempted the reductive Heck reaction between iodide **17** and enone **20**. However, even after extensive experimentation, the desired conjugated product **21** was not formed (Scheme 2). Deiodination of compound **17** was the major undesired pathway, yielding enone **20**. This suggests that while the oxidative addition of the palladium catalyst to alkenyl iodide **17** was occurring, the migratory insertion of the resulting organopalladium intermediate into enone **20** was hindered.

Further insights into the lack of the desired reactivity were gained through single-crystal X-ray diffraction (SCXD) analysis of enone **20** (CCDC number of compound **20**: 2385997). Contrary to our initial predictions, the SCXD data revealed that compound **20** adopts a conformation where the Boc-protected pyrrolidine moiety is positioned pseudo-axially, while the two silyl ether groups are arranged pseudo-equatorially (Scheme 3). Solution phase DFT-calculations of enone **20** also corroborated this conformational preference (see the ESI for details†). In this conformation, the approach of the alkenylpalladium species from the top face would be inhibited by steric hindrance caused by the bulky Boc-protected pyrrolidine moiety and the unfavored twist boat-like transition state. The absence of the reductive Heck product with an (*S*)-configuration at the connection junction suggests that the approach of the organopalladium intermediate from the bottom face is also hindered, presumably due to the presence of the silylether group.

These observations made it clear that we needed to induce a ring flip in the conformation of the reductive Heck acceptor enone to achieve the desired reactivity with the correct stereochemistry. Historically, there have been elegant examples where an energetically less favorable conformation was induced through transitory covalent bond formation to achieve the desired reactivity and selectivity.[31–35] Inspired by these precedents, we envisioned tethering the two hydroxyl groups in compound **20** to enforce their axial positioning. To accomplish this, we designed silyl-tethered enone compound **22** to promote a ring flip. We anticipated that this silyl-tethered compound would adopt a conformation in which the Boc-protected pyrrolidine group is positioned pseudo-equatorially (Scheme 3). Indeed, SCXD analysis of the α-iodinated derivative of **22** confirmed that the silyl-tethered enone adopts the desired ring-flipped conformation (CCDC number of compound **23**: 2385995). With this newly designed silyl-tethered reductive Heck acceptor enone **22**, we predicted an unhindered approach of the alkenylpalladium species from the top face of it, complying with a Fürst–Plattner rule, to yield the desired types A and B connections present in flueggenine A (**6**) and 15′-*epi*-flueggenine D (**7**).

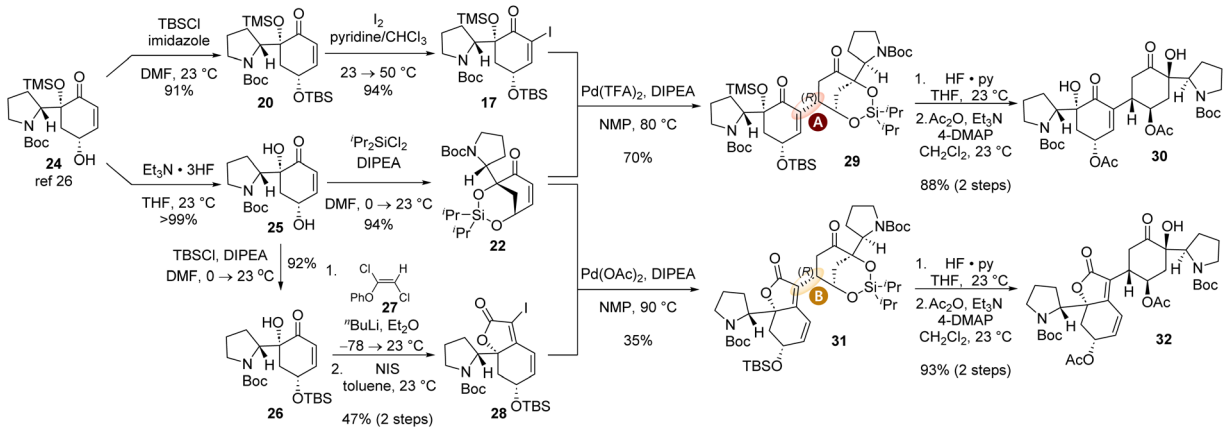


Scheme 3 Conformational analysis of **20** and design of the silyl-tethered enone **22** for the reductive Heck reaction.

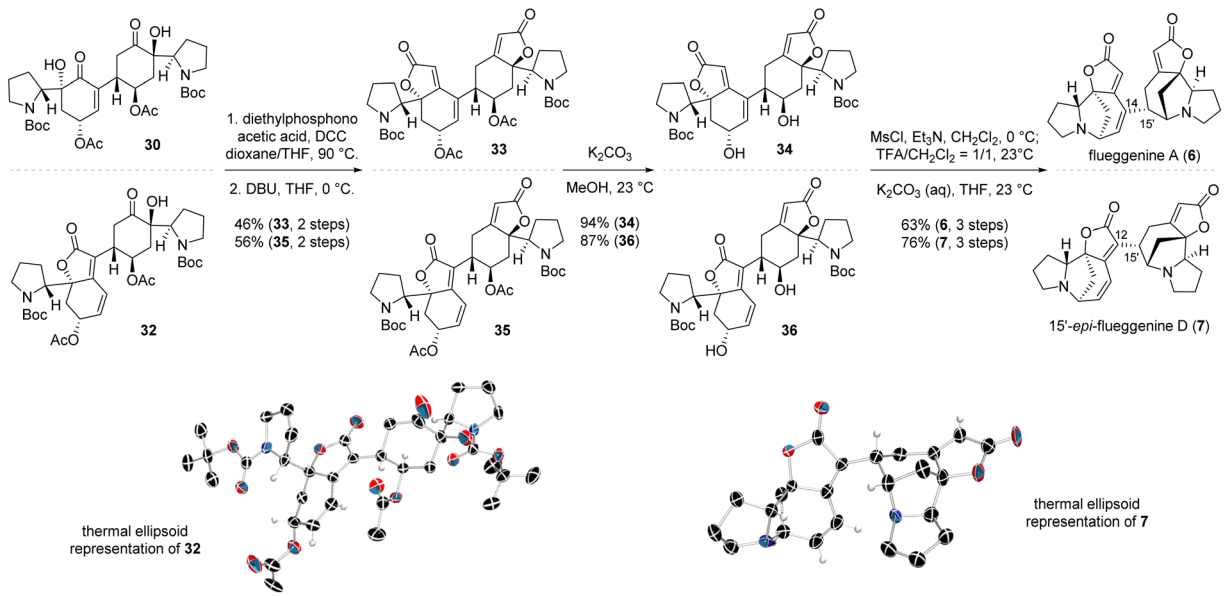
With the new design of tethered reductive Heck acceptor enone **22**, we embarked on the total synthesis of both (−)-flueggenine A (**6**) and (−)-15′-*epi*-flueggenine D (**7**). The synthesis of reductive Heck reaction coupling partners commenced with our previously accessed γ-hydroxyenone compound **24**.[26] For the synthesis of α-iodoenone **17**, γ-hydroxyenone **24** was subjected to a two-step protocol involving TBS protection of the hydroxyl group (91% yield) and α-iodination of the enone moiety with iodine in pyridine and chloroform co-solvent (94% yield). The synthesis of silyl tethered enone **22** was achieved by first removing the TMS group of **24** in the presence of triethylamine trihydrofluoride to yield diol **25** in >99% yield (Scheme 4). Diol **25** was subsequently allowed to react with dichlorodiisopropylsilane in the presence of DIPEA to produce the key silyl tethered enone **22** in 94% yield. The synthesis of iodobutenolide compound **28** involved selective TBS protection of the secondary allylic hydroxyl group in diol **25**. The resulting ketone compound **26** was reacted with lithium phenoxyacetylide generated *in situ* from phenoxy dichloroethene **27** to yield the propargylic alcohol intermediate. This 1,2-addition product was subsequently allowed to react with *N*-iodosuccinimide (NIS) to yield iodobutenolide **28** *via* a presumed iodo-Meyer–Schuster rearrangement in 47% yield over two steps.[27,36,37] The structure of iodide **28** was corroborated by SCXD analysis (CCDC number of compound **28**: 2385999).

With iodoenone **17** and silyl tethered enone **22** in hand, we executed the key reductive Heck reaction in the presence of $Pd(TFA)_2$ and DIPEA. To our utmost delight, the desired reductive Heck product **29** with the (*R*)-configuration at the connection junction (type A connection) was obtained in 70% yield consistent with our stereochemical model (Schemes 3 and 4). HF·pyridine-mediated global desilylation of compound **29** and subsequent acetylation of the resulting product afforded diacetate **30** in 88% yield over two steps. To our pleasure, iodobutenolide **28** and silyl tethered enone **22** successfully furnished conjugated product **31** with type B connectivity in the presence of $Pd(OAc)_2$ and DIPEA in 35% yield. When silyl ether **31** was subjected to the aforementioned desilylation and acetylation protocol, acetylated compound **32** was obtained in 93% yield over two steps. The structure of compound **32** was unambiguously conformed by its SCXD analysis (Scheme 5, CCDC number of compound **32**: 2386004).

The end-game of the synthetic campaign toward (−)-flueggenine A (**6**) involved parallel installation of the butenolide moiety and intramolecular *N*-alkylation to construct the octacyclic framework. The butenolide moiety was introduced by treating diol **30** with diethylphosphonoacetic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC), yielding the HWE precursor. Subsequent reaction of the resulting ester with 1,8-



Scheme 4 Synthesis of the coupling partners for the reductive Heck reaction and its successful execution toward the synthesis of (−)-flueggenine A (**6**) and (−)-15′-*epi*-flueggenine D (**7**).



Scheme 5 Completion of the total synthesis of (−)-flueggenine A (**6**) and (−)-15′-*epi*-flueggenine D (**7**).

diazabicyclo(5.4.0)undec-7-ene (DBU) produced the butenolide compound **33** in 46% yield over two steps (Scheme 5). For the *N*-alkylation, acetate **33** was subjected to methanolysis, yielding diol **34** in 94% yield. The diol moiety was then activated by mesylation. Trifluoroacetic acid (TFA)-mediated Boc-deprotection of the resulting carbamate intermediate, followed by base treatment of the secondary amine, afforded the first synthetic sample of (−)-flueggenine A (**6**) in 63% yield over 3 steps. The spectral data of the synthetic compound matched those of the natural product.[15] To our delight, applying the same end-game protocol to alcohol **32** resulted in the successful synthesis of 15′-*epi*-flueggenine D (**7**) in analogous efficiency compared to the route to (−)-flueggenine A (**6**). The structure of 15′-*epi*-flueggenine D (**7**) was unequivocally corroborated by its SCXD analysis (CCDC number of compound **7**: 2387436).

Conclusions

In conclusion, we have completed the total synthesis of RC-based dimeric securinega alkaloids (−)-flueggenine A (**6**) and (−)-15′-*epi*-flueggenine D (**7**). The key dimerization step was achieved *via* a reductive Heck reaction. The design and employment of silyl-tethered reductive Heck acceptor enone was crucial to achieve the desired reactivity as well as stereoselectivity. This new dimerization strategy, enabling types A and B linkages between norsecurinine monomeric units, combined with existing conjugation chemistry for types C and D connections,[26,27] provides a foundational synthetic solution to access all known RC-based oligomeric securinega alkaloids. Those studies are currently underway in our laboratory and will be the subject of forthcoming reports.

Data availability

The experimental procedures and additional data can be found in the ESI.† Crystallographic data for the structure reported in this article have been deposited at the Cambridge Crystallographic Data Centre, under deposition number 2387436 (**7**), 2385997 (**20**), 2385995 (**23**), 2385999 (**28**), and 2386004 (**32**). Copies of the data can be obtained free of charge from the CCDC *via* **https://www.ccdc.cam.ac.uk/structures/**.

Author contributions

S. M. S. and S. H. conceived the study. S. H. supervised the project. S. M. S. played a key role in experimentation. D. K. performed the single crystal X-ray diffraction analysis. T. K. conducted computational studies. S. H. and S. M. S. wrote the paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

1 E. Chirkin, W. Atkatlian and F.-H. Porée, in *The Alkaloids: Chemistry and Biology*, ed. H.-J. Knölker, Academic Press, London, 2015, ch. 1, pp. 1–120.
2 W. Hou, H. Huang, X.-Q. Wu and J.-X. Lan, Bioactivities and mechanism of action of securinega alkaloids derivatives reported prior to 2022, *Biomed. Pharmacother.*, 2023, **158**, 114190.
3 S. M. Weinreb, Total synthesis of the Securinega alkaloids, *Nat. Prod. Rep.*, 2009, **26**, 758–775.
4 R. Wehlauch and K. Gademann, Securinega Alkaloids: Complex Structures, Potent Bioactivities, and Efficient Total Syntheses, *Asian J. Org. Chem.*, 2017, **6**, 1146–1159.
5 H. Xiao, Q. Zhang, P. Zhong, G. Tang, L. Tao, Z. Huang, D. Guo, Y. Liao, Y. Peng, Z.-L. Wu, Y. Wang, W.-C. Ye and L. Shi, Securinine Promotes Neuronal Development and Exhibits Antidepressant-like Effects *via* mTOR Activation, *ACS Chem. Neurosci.*, 2021, **12**, 3650–3661.
6 Z.-L. Wu, X.-J. Huang, M.-T. Xu, X. Ma, L. Li, L. Shi, W.-J. Wang, R.-W. Jiang, W.-C. Ye and Y. Wang, Flueggeacosines A–C, Dimeric Securinine-Type Alkaloid Analogues with Neuronal Differentiation Activity from Flueggea suffruticosa, *Org. Lett.*, 2018, **20**, 7703–7707.
7 Q.-F. He, Z.-L. Wu, L. Li, W.-Y. Sun, G.-Y. Wang, R.-W. Jiang, L.-J. Hu, L. Shi, R.-R. He, Y. Wang and W.-C. Ye, Discovery of Neuritogenic Securinega Alkaloids from Flueggea suffruticosa by a Building Blocks-Based Molecular Network Strategy, *Angew. Chem., Int. Ed.*, 2021, **60**, 19609–19613.
8 D. E. Olson, Psychoplastogens: A Promising Class of Plasticity-Promoting Neurotherapeutics, *J. Exp. Neurosci.*, 2018, **12**, 1179069518800508.
9 H. N. Saeger and D. E. Olson, Psychedelic-inspired approaches for treating neurodegenerative disorders, *J. Neurochem.*, 2022, **162**, 109–127.
10 S. A. Snyder, A. M. ElSohly and F. Kontes, Synthetic approaches to oligomeric natural products, *Nat. Prod. Rep.*, 2011, **28**, 897–924.
11 H. Zhang, C.-R. Zhang, K.-K. Zhu, A.-H. Gao, C. Luo, J. Li and J.-M. Yue, Fluevirosines A–C: A Biogenesis Inspired Example in the Discovery of New Bioactive Scaffolds from Flueggea virosa, *Org. Lett.*, 2013, **15**, 120–123.
12 H. Zhang, W. Wei and J.-M. Yue, From monomer to tetramer and beyond: the intriguing chemistry of Securinega alkaloids from Flueggea virosa, *Tetrahedron*, 2013, **69**, 3942–3946.
13 H. Zhang, C.-R. Zhang, Y.-S. Han, M. A. Wainberg and J.-M. Yue, New Securinega alkaloids with anti-HIV activity from Flueggea virosa, *RSC Adv.*, 2015, **5**, 107045–107053.
14 H. Zhang, Y.-S. Han, M. A. Wainberg and J.-M. Yue, Anti-HIV Securinega alkaloid oligomers from Flueggea virosa, *Tetrahedron*, 2015, **71**, 3671–3679.
15 L.-S. Gan, C.-Q. Fan, S.-P. Yang, Y. Wu, L.-P. Lin, J. Ding and J.-M. Yue, Flueggenines A and B, Two Novel C,C-Linked Dimeric Indolizidine Alkaloids from Flueggea virosa, *Org. Lett.*, 2006, **8**, 2285–2288.
16 B. E. Hetzler, D. Trauner and A. L. Lawrence, Natural product anticipation through synthesis, *Nat. Rev. Chem*, 2022, **6**, 170–181.
17 M. Kim, S. Park, G. Kang, Y. S. Jang, K. H. Kim, S. Han and C. S. Kim, Natural product anticipation *via* chemical synthesis: Discovery of two new securinega alkaloids, *iScience*, 2024, **27**, 110495.
18 B.-X. Zhao, Y. Wang, C. Li, G.-C. Wang, X.-J. Huang, C.-L. Fan, Q.-M. Li, H.-J. Zhu, W.-M. Chen and W.-C. Ye, Flueggedine, a novel axisymmetric indolizidine alkaloid dimer from Flueggea virosa, *Tetrahedron Lett.*, 2013, **54**, 4708–4711.
19 H. Wei, C. Qiao, G. Liu, Z. Yang and C. Li, Stereoselective Total Syntheses of (−)-Flueggine A and (+)-Virosaine B, *Angew. Chem., Int. Ed.*, 2013, **52**, 620–624.
20 N. Ma, Y. Yao, B.-X. Zhao, Y. Wang, W.-C. Ye and S. Jiang, Total synthesis of securinega alkaloids (−)-norsecurinine, (−)-niruroidine and (−)-flueggine A, *Chem. Commun.*, 2014, **50**, 9284–9287.

21 G. Kang and S. Han, Synthesis of Dimeric Securinega Alkaloid Flueggeacosine B: From Pd-Catalyzed Cross-Coupling to Cu-Catalyzed Cross-Dehydrogenative Coupling, *J. Am. Chem. Soc.*, 2022, **144**, 8932–8937.
22 G. Kang and S. Han, Synthesis of Suffranidine B, *J. Am. Chem. Soc.*, 2023, **145**, 24493–24498.
23 L. Liu, T. L. Olson and J. L. Wood, Total Synthesis of (−)-Flueggeacosine C, *Org. Lett.*, 2024, **26**, 7341–7346.
24 S. Jeon, J. Park and S. Han, Syntheses of Dimeric Securinega Alkaloids, *Synlett*, 2017, **28**, 2353–2359.
25 G. Kang, S. Park and S. Han, Synthesis of High-Order and High-Oxidation State Securinega Alkaloids, *Acc. Chem. Res.*, 2023, **56**, 140–156.
26 S. Jeon and S. Han, An Accelerated Intermolecular Rauhut–Currier Reaction Enables the Total Synthesis of (−)-Flueggenine C, *J. Am. Chem. Soc.*, 2017, **139**, 6302–6305.
27 S. Jeon, J. Lee, S. Park and S. Han, Total synthesis of dimeric Securinega alkaloids (−)-flueggenines D and I, *Chem. Sci.*, 2020, **11**, 10934–10938.
28 J. Park, S. Jeon, G. Kang, J. Lee, M.-H. Baik and S. Han, Dimerization Strategies for the Synthesis of High-Order Securinega Alkaloids, *J. Org. Chem.*, 2019, **84**, 1398–1406.
29 A. Fürst and P. A. Plattner, Über Steroide und Sexualhormone. 160. Mitteilung. 2α, 3α- und 2β, 3β-Oxido-chlolestane; Konfiguration der 2-Oxy-cholestane, *Helv. Chim. Acta*, 1949, **32**, 275–283.
30 S. Mannathan, S. Raoufmoghaddam, J. N. H. Reek, J. G. de Vries and A. J. Minnaard, Palladium(II) Acetate Catalyzed Reductive Heck Reaction of Enones; A Practical Approach, *ChemCatChem*, 2015, **7**, 3923–3927.
31 R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, THE TOTAL SYNTHESIS OF RESERPINE, *J. Am. Chem. Soc.*, 1956, **78**, 2023–2025.
32 H. Todoroki, M. Iwatsu, D. Urabe and M. Inoue, Total Synthesis of (−)-4-Hydroxyzinowol, *J. Org. Chem.*, 2014, **79**, 8835–8849.
33 J. Gong, H. Chen, X.-Y. Liu, Z.-X. Wang, W. Nie and Y. Qin, Total synthesis of atropurpuran, *Nat. Commun.*, 2016, **7**, 12183.
34 J. Zhang, M. Liu, C. Wu, G. Zhao, P. Chen, L. Zhou, X. Xie, R. Fang, H. Li and X. She, Total Synthesis of (−)-Pepluanol B: Conformational Control of the Eight-Membered-Ring System, *Angew. Chem., Int. Ed.*, 2020, **59**, 3966–3970.
35 T. Watanabe, K. Oga, H. Matoba, M. Nagatomo and M. Inoue, Total Synthesis of Taxol Enabled by Intermolecular Radical Coupling and Pd-Catalyzed Cyclization, *J. Am. Chem. Soc.*, 2023, **145**, 25894–25902.
36 S. Puri, N. Thirupathi and M. Sridhar Reddy, Iodo Meyer–Schuster Rearrangement of 3-Alkoxy-2-yn-1-ols for β-Mono (Exclusively Z-Selective)-/Disubstituted α-Iodo-α,β-Unsaturated Esters, *Org. Lett.*, 2014, **16**, 5246–5249.
37 M. S. Reddy, N. Thirupathi, M. Hari Babu and S. Puri, Synthesis of Substituted 3-Iodocoumarins and 3-Iodobutenolides *via* Electrophilic Iodocyclization of Ethoxyalkyne Diols, *J. Org. Chem.*, 2013, **78**, 5878–5888.