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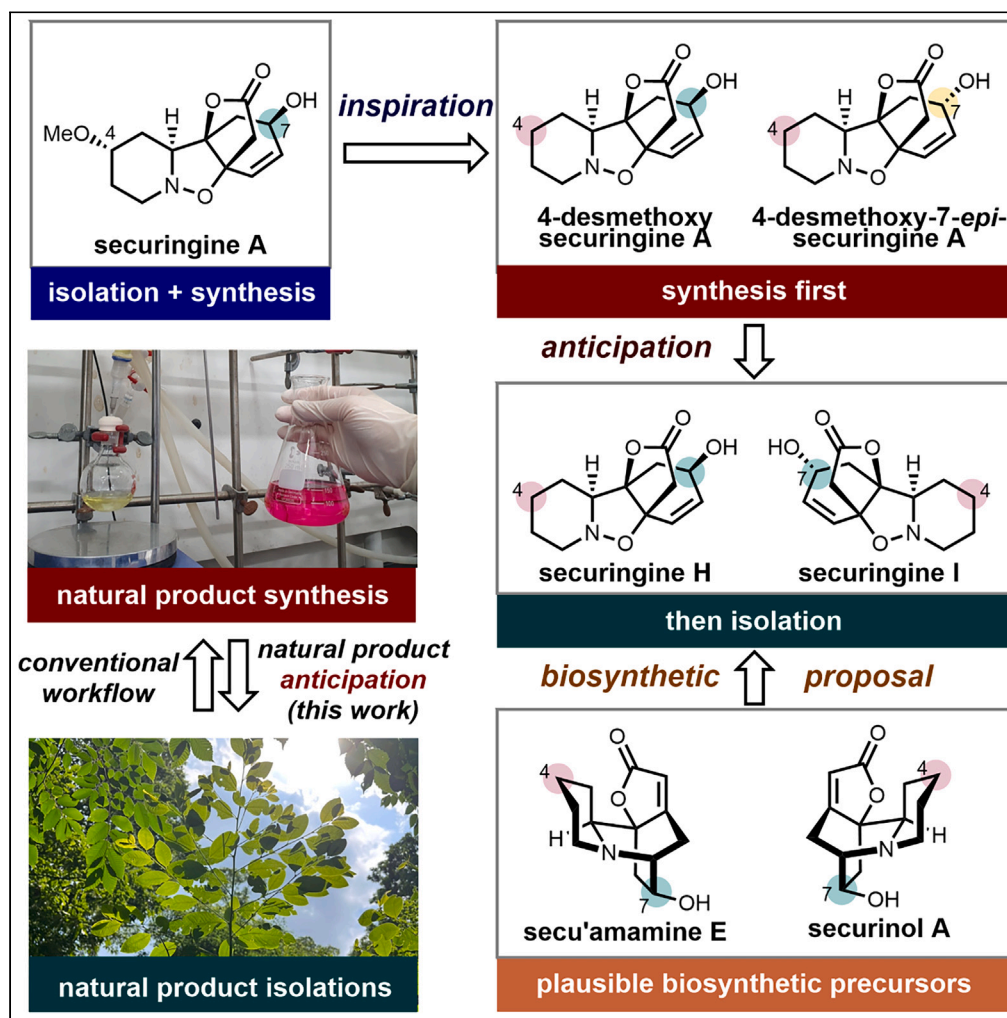
Article

Natural product anticipation via chemical synthesis: Discovery of two new securinega alkaloids

Minji Kim, Sangbin Park, Gyumin Kang, Yoon Seo Jang, Ki Hyun Kim, Sunkyu Han, Chung Sub Kim

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Highlights

Synthesis of desmethoxysecuringine A derivatives as anticipated natural products

Isolation of new natural products securingines H and I from *Flueggea suffruticosa*

Structure assignments of isolated securingines H and I based on synthetic samples

Biosynthetic hypothesis for securingines H and I

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Natural product anticipation via chemical synthesis: Discovery of two new securinega alkaloids

Minji Kim,[1,4] Sangbin Park,[2,4] Gyumin Kang,[2,4] Yoon Seo Jang,[3,4] Ki Hyun Kim,[3,*] Sunkyu Han,[2,*] and Chung Sub Kim[1,3,5,*]

SUMMARY

The isolation of a natural product conventionally precedes its chemical synthesis. Often, the isolation and structure determination of a natural product present in minute quantities in its natural source pose formidable challenges, akin to finding "a needle in a haystack." On the other hand, leveraging plausible biosynthetic insights and biomimetic synthetic expertise would allow for the prior synthesis of presumed natural products, followed by their verification in natural sources. In this study, we unveil two novel securinega alkaloids, securingines H and I, employing the natural product anticipation through synthesis approach. Structural analysis of securingines H and I suggests that they are biosynthetic derivatives of secu'amamine E and securinol A, respectively. We posit that this "synthesis first" strategy represents a valuable approach to the discovery of new natural products.

INTRODUCTION

Total synthesis of natural products has enabled the discovery of new chemical reactivity, the testing of utility and robustness of existing synthetic methods, and the development of natural product-based drugs.[1–3] The field of total synthesis owes much to the dedicated efforts of natural product chemists, who have unearthed structurally intriguing and biologically active compounds. The traditional workflow has involved a sequential process: natural product chemists first isolate and elucidate the structure of secondary metabolites, followed by synthetic organic chemists undertaking their chemical synthesis. Contrary to the conventional workflow, there have been cases where the chemical synthesis of natural products preceded their discovery from natural sources. These "natural product anticipations" have been particularly noteworthy in synthetic campaigns guided by biosynthetic logic (Figure 1A).[4]

Securinega alkaloids are natural products with a basic tetracyclic framework comprising butenolide and tertiary amine moieties. This family of natural products has drawn immense interests from the synthetic community due to their intriguing architecture and prominent biological activities.[5–9] Notably, the A-ring of the basic securinega skeleton undergoes biosynthetic oxidation to diversify its structural portfolio.[10] Among these, the oxidation at the C4-position is the most frequently observed oxidation pattern.[10] For example, both allosecurinine (**1**, not possessing the C4-methoxy group)[11] and securitinine (**2**, possessing the C4-methoxy group)[12] have been isolated from *Flueggea suffruticosa* (Pall.) Baill (Figure 1B). Similarly, both phyllantidine (**3**, the 1,2-Meisenheimer rearrangement product of the *N*-oxide derivative of allosecurinine)[13] and its C4-methoxy congener secu'amamine D (**4**)[14] have been discovered.

In 2019, the Lee group reported the isolation of securingine A from the twigs of *F. suffruticosa*.[15] Subsequently, the Han group proposed a calculation-assisted stereochemical revision of securingine A.[16] In 2022, Han and coworkers completed the total synthesis of securingine A (**5**) and experimentally confirmed its revised structure.[17] Considering the isolations of both 4-methoxy and 4-desmethoxy congeners from *F. suffruticosa* (Figure 1B), we anticipated that the 4-desmethoxy analogs of securingine A (**5**) might be present in the natural source. With a robust synthetic route to securingine A established,[17] we envisioned to synthesize its 4-desmethoxy counterparts such as 4-desmethoxysecuringine A (**6**) and 4-desmethoxy-7-*epi*-securingine A (**7**) and investigate their presence in the twigs of *F. suffruticosa*. Here, we delineate the discovery of two new securinega alkaloids securingines H (**6**) and I (**8**) that were enabled by natural product anticipation through synthesis approach (Figure 1B).

RESULTS AND DISCUSSION

Synthesis of the 4-desmethoxy congeners of securingine A commenced from allosecurinine (**1**), the most abundant natural product in the roots of *F. suffruticosa*. By employing our previously developed extraction protocols, 11 g of allosecurinine was secured from 2 kg of the roots

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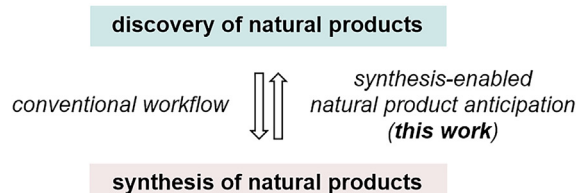[4]These authors contributed equally
[5]Lead contact
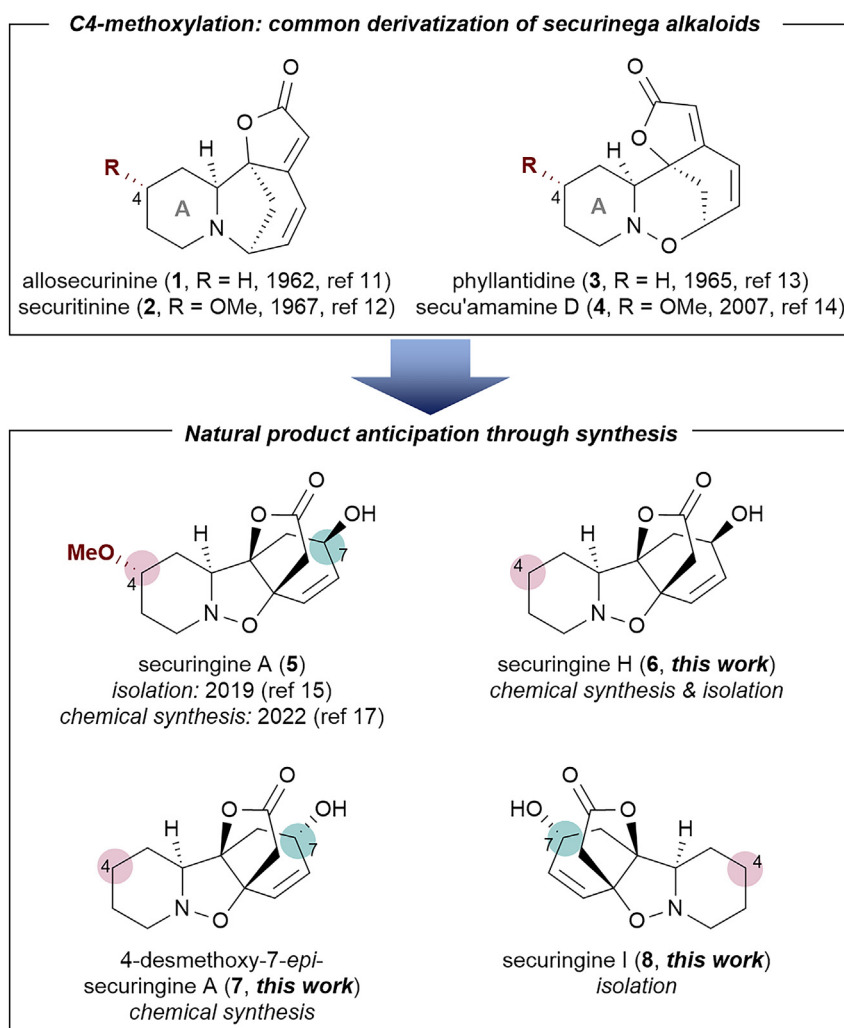*Correspondence: khkim83@skku.edu (K.H.K.), sunkyu.han@kaist.ac.kr (S.H.), chungsub.kim@skku.edu (C.S.K.)
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A *Relationship between natural product isolations and chemical synthesis.*

discovery of natural products

conventional workflow   *synthesis-enabled
natural product anticipation
(this work)*

synthesis of natural products

B *C4-methoxy and C4-desmethoxy securinega alkaloids.*

C4-methoxylation: common derivatization of securinega alkaloids

allosecurinine (**1**, R = H, 1962, ref 11)
securitinine (**2**, R = OMe, 1967, ref 12)

phyllantidine (**3**, R = H, 1965, ref 13)
secu'amamine D (**4**, R = OMe, 2007, ref 14)

Natural product anticipation through synthesis

securingine A (**5**)
*isolation: 2019 (ref 15)
chemical synthesis: 2022 (ref 17)*

securingine H (**6**, *this work*)
chemical synthesis & isolation

4-desmethoxy-7-*epi*-
securingine A (**7**, *this work*)
chemical synthesis

securingine I (**8**, *this work*)
isolation

Figure 1. Securingine A-inspired natural product anticipation via chemical synthesis
(A) Relationship between natural product isolations and chemical synthesis.
(B) C4-methoxy and C4-desmethoxy securinega alkaloids.

of *F. suffruticosa* in a single pass.[18,19] Treatment of allosecurinine (**1**) with FmocCl and potassium carbonate induced its deconstructive functionalization to yield C–N cleaved product **9** in 96% yield (Scheme 1A).[20,21] When allylic chloride derivative **9** was allowed to react with silver tetrafluoroborate in acetone and water cosolvent,[20] allylic alcohol products **10** and **11** were obtained in 35% and 58%, respectively. Subsequent 1,8-diazabicyclo[5.4.0]undec-7-ene-mediated Fmoc deprotection of **10** followed by a Gademann's intramolecular *aza*-Michael addition of the resulting secondary amine derivative produced secu'amamine E (**12**) in 86% yield.[22] Treatment of secu'amamine E (**12**) with *m*CPBA and potassium carbonate forged oxidatively rearranged product **6**, 4-desmethoxysecuringine A, in 66% yield.

A *Synthesis of natural product candidates 6 and 7.*
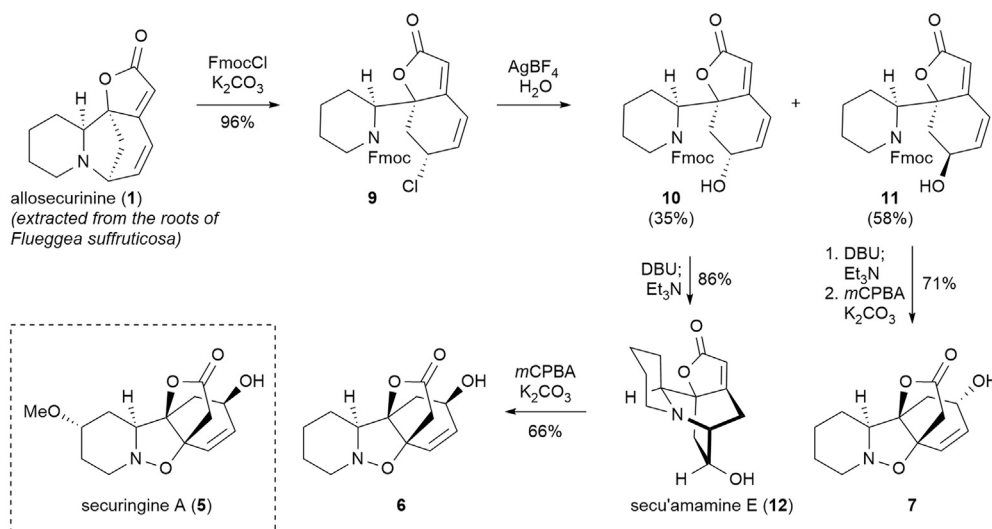
B *Mechanism for the transformation of 12 to 6.*
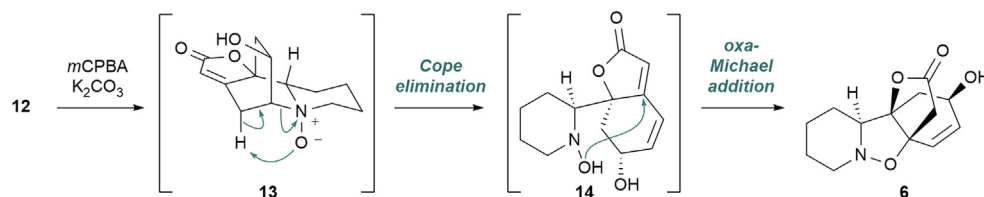
Scheme 1. Synthesis of anticipated natural products 6 and 7
(A) Synthesis of natural product candidates **6** and **7**.
(B) Mechanism for the transformation of **12** to **6**.

A plausible reaction mechanism for the transformation of secu'amamine E (**12**) to compound **6** is depicted in Scheme 1B.[17] Reaction of secu'amamine E (**12**) with *m*CPBA would result in the formation of *N*-oxide intermediate **13**. *N*-oxide **13** then undergoes a Cope elimination, resulting in the formation of hydroxylamine intermediate **14**. Subsequent intramolecular 1,4-conjugate addition of the hydroxylamine moiety in **14** leads to the synthesis of 4-desmethoxysecuringine A (**6**). Similarly, compound **11** was transformed into oxidative rearrangement product **7** via the same sequence of reactions.

With anticipated natural products **6** and **7** in hand, our next step was verifying their presence in *F. suffruticosa*. To accomplish this, we first extracted *F. suffruticosa* twigs with 80% methanol from which diverse securinega alkaloids have been isolated.[15] The resulting methanol extract was analyzed by liquid chromatography-mass spectrometry, and the extracted ion chromatograms with *m/z* 252 showed two peaks consistent with those of synthetic **6** and **7** (Figure S1). Furthermore, high-resolution tandem mass spectrometry fragmentation patterns of these two natural products and the corresponding synthetic **6** and **7** were identical. Encouraged by this observation, our subsequent objective was to isolate these two natural products from the crude extract of *F. suffruticosa*. The methanol extract was then dissolved in water and partitioned with chloroform, and the resulting chloroform extract was subjected to repeated mass spectrometry (MS)-guided column chromatography including semi-preparative high-performance liquid chromatography (HPLC) (Scheme 2A). As a result, we obtained ~0.1 mg each of the two natural products and named them securingines H and I.

Significantly, the natural securingine H and its synthetic counterpart, compound **6**, displayed indistinguishable HPLC traces, MS/MS data, ^{1}H-NMR spectra, and electronic circular dichroism (ECD) spectra (Scheme 2B and 2C). Consequently, it is unambiguously established that securingine H (**6**) and synthetic compound **6** are identical compounds. This reaffirmed that the anticipated natural product, namely 4-desmethoxysecuringine A, is present in nature. In the case of securingine I, while its HPLC trace (achiral column), MS/MS data, and ^{1}H-NMR spectrum were identical to those of synthetic compound **7**, its ECD spectrum exhibited a mirror image compared to that of synthetic **7**. These data indicate that securingine I (**8**) is the enantiomer of synthetic compound **7**.

A plausible biosynthetic hypothesis for allosecurinine (**1**), securingines H (**6**), and I (**8**) is presented in Scheme 3. Notably, menisdaurilide (**15**) was isolated from the extracts of twigs of *F. suffruticosa* in an enantiomerically enriched form. Its (6*R*, 8*S*) configurations were confirmed by ECD spectra comparison of natural and synthetic samples of menisdaurilide (**15**, Figure S4). Hence, we conjectured that the configuration of the allylic alcohol moiety is conserved during the biosynthesis of downstream securinega alkaloids. In 2008, Busqué, de March and coworkers
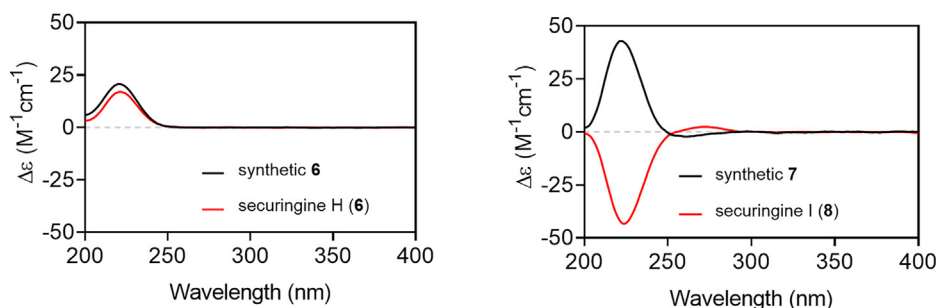
A *Isolation of securingines H and I.*
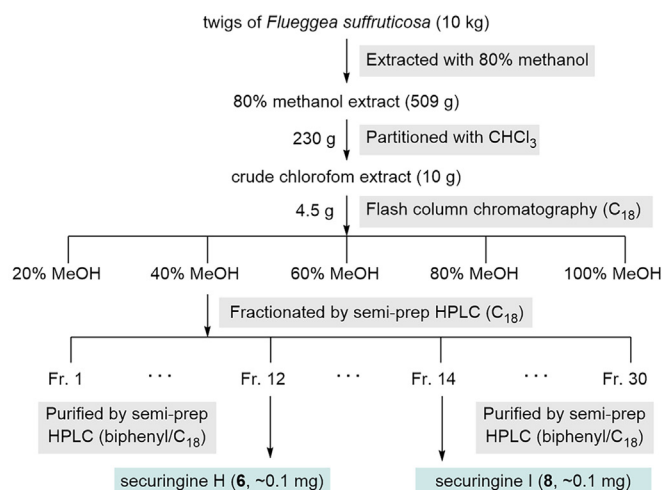
B *Structure identification of securingines H and I.*
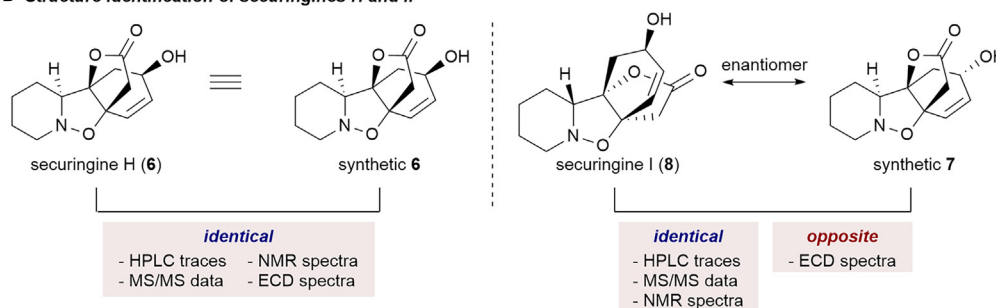
C *Comparison of ECD spectra of synthetic 6, 7 & securingines H, I.*

Scheme 2. Isolation of securingines H (6) and I (8) and their structure assignments based on synthetic compounds 6 and 7

(A) Isolation for securingines H and I.

(B) Structure identification of securingines H and I.

(C) Comparison of ECD spectra of synthetic 6, 7, & securingines H, L.

proposed that the biosynthesis of securinine-type alkaloids involves a nucleophilic addition of the menisdaurilide derivative to 1-piperideine.[23] The vinylogous Mannich reaction and subsequent *aza*-Michael addition between the enol tautomer of menisdaurilide and 1-piperideine (**16**) would proceed via either TS-A or TS-B. The approach of 1-piperideine (**16**) from the *anti*-face of the alcohol moiety of the menisdaurilide derivative (TS-A) would yield secu'amamine E (**12**, Scheme 3). *N*-oxidation of secu'amamine E (**12**) followed by a Cope elimination and a 1,4-conjugate addition of the resulting hydroxylamine group would result in securingine H (**6**). The antiperiplanar configuration between the amine and the hydroxyl moieties would also enable a 1,2-amine shift reaction as proposed by Gademann and coworkers to yield allo-securinine (**1**).[22]

On the other hand, the approach of 1-piperideine from the *syn*-face of the alcohol moiety of the menisdaurilide derivative (TS-B) leads to the formation of securinol A (**17**). The biosynthesis of securingine I (**8**) can be attributed to the *N*-oxidation of securinol A (**17**), followed by a Cope elimination reaction and a 1,4-conjugate addition of the resulting hydroxylamine group. In contrast to secu'amamine E (**12**), the
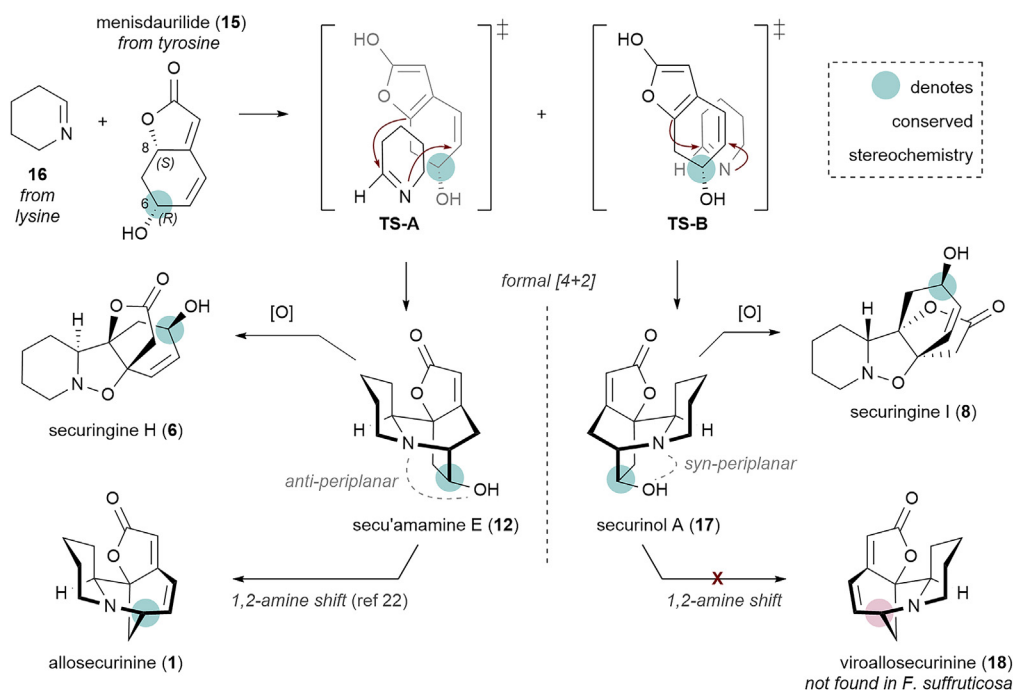
Scheme 3. The biosynthetic hypothesis for securingines H (6), I (8), and allosecurinine (1)

synperiplanar configuration between the amine moiety and the hydroxyl group in securinol A (**17**) renders the 1,2-amine shift less feasible.[22] This proposed biosynthetic pathway aligns with the absence of viroallosecurinine (**18**) in *F. suffruticosa*.

Two novel securinega alkaloids, securingines H (**6**) and I (**8**), have been discovered via the "natural product anticipation through synthesis" strategy. Leveraging our biomimetic synthetic expertise in securinega alkaloids,[9,17] we successfully synthesized 4-desmethoxy derivatives of securingine A, namely compounds **6** (4-desmethoxysecuringine A) and **7** (4-desmethoxy-7-*epi*-securingine A), anticipating them as natural products. Subsequent investigations of *F. suffruticosa* twigs unveiled that compound **6** and *ent*-**7** are, indeed, natural products—securingines H and I, respectively—present in this plant. From a biosynthetic standpoint, secu'amamine E (**12**) and securinol A (**17**), both stemming from 1-piperideine and menisdaurilide, would serve as precursors for securingines H (**6**) and I (**8**), respectively. It is crucial to emphasize that the detection and isolation of minute amounts of each natural product in *F. suffruticosa* posed a significant challenge, and the discovery of these compounds would have been exceedingly difficult without employing the natural product anticipation through synthesis approach.

Limitations of the study

Although the natural product anticipation strategy proposed by us led to the discovery of natural products that exist in a fractional amount in the natural source, this strategy might not be applicable for the discovery of biosynthetic intermediate (i.e., natural product) that undergoes rapid transformation into downstream natural products. Also, if the proposed biosynthetic sequence does not match the actual biosynthetic pathway (for example, if the C4-methoxylation of the securinega alkaloids occurs prior to the generation of azabicyclo[2.2.2]octane core), it cannot lead to the discovery of natural product.

STAR★METHODS

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- METHOD DETAILS
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  - Isolation of securingines H (**6**) and I (**8**) from the twigs of *F. suffruticosa*
  - Experimental procedures for the synthesis of (+)-ε-chloro butenolide **9**

SUPPLEMENTAL INFORMATION

ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

S.H., C.S.K., and G.K. conceived the research; S.H., C.S.K., K.H.K., and G.K. designed the experiments; chemical syntheses were conducted by S.P. and G.K.; M.K. performed the natural product isolations and structure elucidations; Y.S.J. performed natural product analysis; and all authors wrote and proofread the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
allosecurinine (1)	Kang et al.[18]	CAS: 884-68-4
fluorenylmethyloxycarbonyl chloride	Alfa Aesar	CAS: 28920-43-6
potassium carbonate	Daejung	CAS: 584-08-7
silver tetrafluoroborate	Sigma-Aldrich	CAS: 14104-20-2
1,8-diazabicyclo[5.4.0]undec-7-ene	TCI	CAS: 6674-22-2
Triethylamine	Sigma-Aldrich	CAS: 121-44-8
3-chloroperoxybenzoic acid	Sigma-Aldrich	CAS: 937-14-4
TBDPS-protected menisdaurilide (20)	Park et al.[17]	CAS: 1067651-08-4
acetic acid	Sigma-Aldrich	CAS: 64-19-7
tetrabutylammonium fluoride	Sigma-Aldrich	CAS: 429-41-4

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Chung Sub Kim (chungsub.kim@skku.edu).

Materials availability

All data supporting the newly synthesized compounds can be found within the manuscript and the supplemental information or can be received from the lead contact upon request.

Data and code availability

This paper does not report original code.

Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

METHOD DETAILS

General information

All reactions were performed in oven-dried or flame-dried round-bottomed flasks and vials. Unless otherwise noted, the flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon, and vials were tightly sealed with plastic septa, Teflon tape, and parafilm. Stainless steel syringes were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using silica gel (60-Å pore size, 40–63 μm, 4-6% H_2O content, Merck).[24] Analytical thin–layer chromatography (TLC) was performed using glass plates pre-coated with 0.25 mm silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light, and/or a basic aqueous potassium permanganate ($KMnO_4$) solution.

Unless otherwise stated, all commercial reagents and solvents were used without additional purification with the following exceptions as indicated below. Dichloromethane and tetrahydrofuran were purchased from Merck and Daejung Inc., respectively and were purified by the method of Grubbs et al. under positive argon pressure.[25]

^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded with Bruker AVANCE III HD Nanobay (400 MHz), Bruker AVANCE III HD (400 MHz), Bruker AVANE NEO Nanobay (400 MHz), Bruker Avance NEO (500 MHz), Agilent DD-2 (600 MHz) or Bruker AVANCE III (700 MHz) and calibrated by using the residual undeuterated chloroform (δ_H = 7.26 ppm) and $CDCl_3$ (δ_C = 77.23 ppm) as internal references. Data are reported in the following manners: chemical shift in ppm [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, app = apparent, br = broad), coupling constant(s) in Hertz, integration]. The NMR solvent $CDCl_3$ was taken from a stock containing anhydrous K_2CO_3 to remove residual DCl. High resolution mass spectra of synthetic compounds were obtained from KAIST Analysis Center for Research Advancement (Daejeon) by using ElectroSpray Ionization (ESI) or Atmospheric Solids Analysis Probe (ASAP) ionization method. Specific rotation $[\alpha]_D^T$ was obtained by JASCO P-2000 polarimeter. Electronic circular dichroism (ECD) spectra were measured on a JASCO J-1500 CD spectrometer (JASCO, Easton, MD, USA).

HRESIMS spectra of natural securingines H and I were obtained using an Agilent G6545B quadrupole time-of-flight mass spectrometer (Agilent Technologies) coupled to an Agilent 1260 Infinity II series furnished with a 6545 LC-Q-TOF mass spectrometer (Agilent Technologies) with an Waters ACQUITY UPLC® BEH C_{18} column (150 × 2.1 mm i.d, 1.7 μm; flow rate: 0.3 mL/min). The LC-MS analysis was performed on an Agilent 1260 series HPLC system with a diode array detector and a 6130 series ESI mass spectrometer equipped with an analytical Kinetex C_{18} 100 Å column (250 mm × 4.6 mm i.d., 5 μm; flow rate: 0.7 mL/min). Semipreparative high-performance liquid chromatography (HPLC) was conducted using an Agilent 1260 pump, which was equipped with a Luna C_{18}(2) 100 Å column (250 mm × 10 mm i.d., 10 μm; flow rate: 4.0 mL/min) and Kinetex Biphenyl 100 Å column (250 mm × 10 mm i.d., 5 μm; flow rate: 4.0 mL/min). Flash column packed with reversed-phased (RP)-C_{18} silica gel (230–400 mesh, Merck, Germany) was implemented.

UPLC condition was set with a Waters ACQUITY UPLC® BEH C18 column (150 × 2.1 mm i.d, 1.7 μm) with a gradient system of 5 – 50 % MeCN (flow rate 0.3 mL/min for 20 min). The parameters of MS & MS/MS were as follows: ion mode, positive-ion mode; gas temperature, 320°C; gas flow, 8 L/min; nebulizer pressure, 35 psi; sheath gas temperature, 350°C; sheath gas flow, 11 L/min; capillary voltage, 3500 V; nozzle voltage, 1000 V; fragmentor voltage, 100 V; MS range, 100 – 1700 m/z; MS Acquisition rate, 1 spectra/s; MS Acquisition time 1000 ms/spectrum; MS/MS range, 100 – 1700; MS/MS acquisition rate, 1 spectra/s; MS/MS acquisition time, 1000 ms/spectrum; collision energy fixed, 10, 20, 40 eV. Internal references (purine and HP-0921) were adopted to modify the measured masses in real-time. The reference masses were obtained at m/z 121.0508, 322.0481, 922.0097 in the positive-ion mode, respectively.

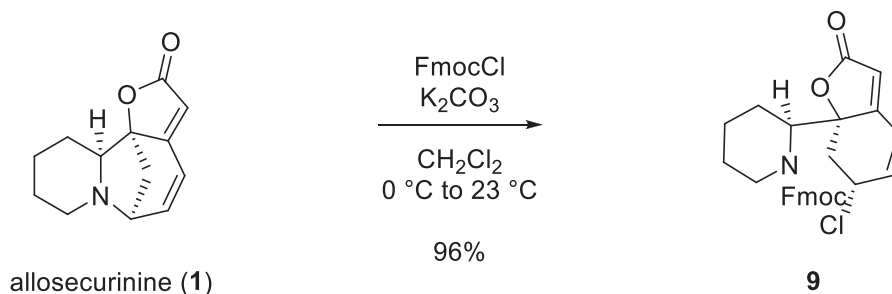### Isolation of securingines H (6) and I (8) from the twigs of *F. suffruticosa*

The twigs of *F. suffruticosa* were obtained in November 2023 from Goesan, Korea, and were authenticated by one of the authors (C.S.K.). A voucher specimen of the plant (SKKU-NPCB-2023-01) has been stored at the School of Pharmacy, Sungkyunkwan University, Suwon, Korea.

The twigs of *F. suffruticosa* (10 kg) were extracted twice with 80% aqueous MeOH at room temperature and filtered. The filtrate was concentrated under a reduced pressure to obtain a crude MeOH extract (509 g). The crude (230 g) was then suspended in deionized water and partitioned with $CHCl_3$, yielding 10 g of extract. The $CHCl_3$-soluble fraction (4.5 g) was subjected to passage over an RP-C_{18} silica gel open column, eluting with 20%, 40%, 60%, 80%, and 100% MeOH to give 5 fractions. 40% MeOH fraction was further fractionated by a semipreparative HPLC system (Phenomenex, Luna 10 μm C_{18}(2) 250 × 10 mm i.d.) with a gradient elution from 10% to 50% aqueous MeCN with 0.01% TFA over 30 min (flow rate: 4 mL/min) to give 30 fractions. Subfraction 12 was separated by semipreparative HPLC (Phenomenex, Kinetex 5 μm Biphenyl 250 × 10 mm i.d.) with a gradient system of 10–30% MeCN with 0.01% TFA (flow rate 4 mL/min for 30 min) to afford a mixture containing securingine H (t_R 14.1 min). This was then purified via semipreparative HPLC (Phenomenex, Luna 10 μm C_{18}(2) 250 × 10 mm i.d.) with a gradient system of 15–27% MeCN with 0.01% TFA (flow rate 4 mL/min for 30 min) to afford securingine H (~0.1 mg, t_R 14.7 min). Subfraction 14 was separated by semipreparative HPLC (Phenomenex, Kinetex 5 μm Biphenyl 250 × 10 mm i.d.) with a gradient system of 18–25% MeCN with 0.01% TFA (flow rate 4 mL/min for 30 min) to afford a mixture containing securingine I (t_R 10.4 min). This was further purified via semipreparative HPLC (Phenomenex, Luna 10 μm C_{18}(2) 250 × 10 mm i.d.) with a gradient system of 18–23% MeCN with 0.01% TFA (flow rate 4 mL/min for 30 min) to afford securingine I (~0.1 mg, t_R 16.9 min). Natural menisdaurilide previously isolated from *F. suffruticosa* was provided by Prof. Kang Ro Lee, Sungkyunkwan University.[15]

Securingine H (**6**): white powder; UV (MeCN/H_2O) λ_{max} 224 nm; ECD (MeOH) λ_{max} (Δε) 221 (-41.64) nm; ^{1}H NMR (700 MHz, CDCl$_3$) δ 6.10 (dd, J = 10.1, 2.8 Hz, 1H), 5.92 (dd, J = 10.1, 1.8 Hz, 1H), 4.39 (m, 1H), 3.41 (dt, J = 8.5, 2.7 Hz, 1H), 3.05 (d, J = 18.9 Hz, 1H), 2.73 (d, J = 18.8 Hz, 1H), 2.42 (m, 2H), 2.04 (dd, J = 11.7, 2.5 Hz, 1H), 1.88 (m, 2H), 1.80 (m, 2H), 1.65 (m, 2H), 1.21 (dt, J = 13.0, 4.2 Hz, 1H); HRESIMS (positive-ion mode) m/z 252.1234 $[M + H]^+$ (calcd for $C_{13}H_{18}NO_4^+$, 252.1230).

Securingine I (**8**): white powder; UV (MeCN/ H_2O) λ_{max} 222 nm; ECD (MeOH) λ_{max} (Δε) 272 (-0.10), 224 (16.39) nm; ^{1}H NMR (700 MHz, CDCl$_3$) δ 6.02 (dd, J = 10.2, 1.9 Hz, 1H), 5.93 (dd, J = 10.3, 2.1 Hz, 1H), 4.40 (m, 1H), 3.43 (m, 1H), 3.11 (d, J = 18.9 Hz, 1H), 2.58 (d, J = 18.9 Hz, 1H), 2.51 (ddd, J = 12.1, 9.0, 3.0 Hz, 1H), 2.45 (dd, J = 13.6, 4.9 Hz, 1H), 2.18 (dd, J = 11.7, 2.4 Hz, 1H), 1.89 (m, 1H), 1.79 (m, 2H), 1.72 (m, 1H), 1.57 (m, 2H), 1.24 (m, 1H); HRESIMS (positive-ion mode) m/z 252.1251 $[M + H]^+$ (calcd for $C_{13}H_{18}NO_4^+$, 252.1230).

Experimental procedures for the synthesis of (+)-ε-chloro butenolide 9

allosecurinine (**1**) → [FmocCl, K_2CO_3, CH_2Cl_2, 0 °C to 23 °C, 96%] → **9**

Fluorenylmethyloxycarbonyl chloride (302 mg, 1.167 mmol, 1.5 equiv.) was added to a solution of allosecurinine (**1**) (169 mg, 0.778 mmol, 1.0 equiv.) in dichloromethane (7.8 mL) at 0°C. Then, potassium carbonate (322 mg, 2.333 mmol, 3.0 equiv.) was added at 0°C and the resulting mixture was slowly warmed to 23°C. After 5 h, the reaction was quenched with ammonium chloride (10 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined organic layer was dried ov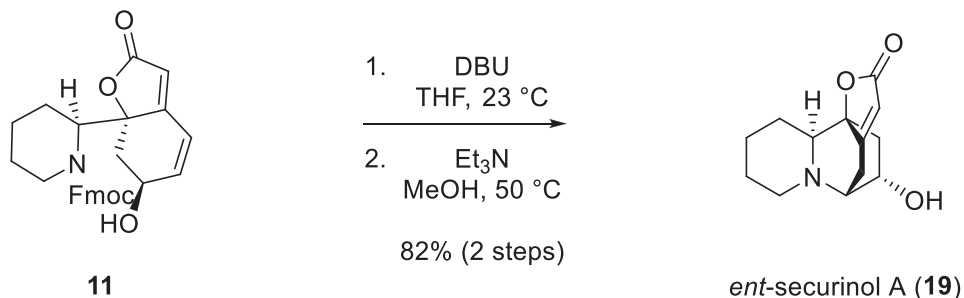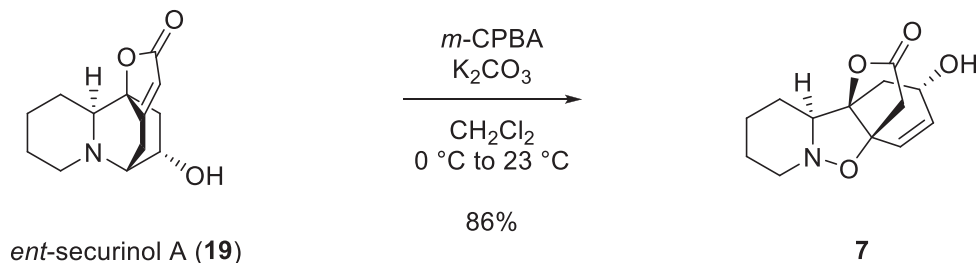er anhydrous sodium sulfate. The resulting filtrate was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel: diam. 2.5 cm, ht. 13 cm; eluent: acetone : hexanes = 1 : 6) to afford **9** (356 mg, 96%) as a white solid.

Experimental procedures for the synthesis of ε-hydroxy butenolides (–)-10 and (–)-11

A solution of silver tetrafluoroborate (290 mg, 1.491 mmol, 2.0 equiv.) in distilled water (7.5 mL) was added to a solution of **9** (355 mg, 0.746 mmol, 1.0 equiv.) in acetone (7.5 mL) and the resulting mixture was heated to 50°C under light blocked condition by aluminium foil. After 12 h, the reaction was quenched with brine (10 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined organic layer was dried over anhydrous sodium sulfate. The resulting filtrate was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel: diam. 2.5 cm, ht. 14 cm; eluent: acetone : hexanes = 1 : 4) to afford **10** (120 mg, 35%) as a white solid and **11** (199 mg, 58%) as a white solid.

Experimental procedures for the synthesis of (–)-secu'amamine E (12)

1,8-Diazabicyclo[5.4.0]undec-7-ene (44 μL, 0.295 mmol, 5.0 equiv.) was added to a solution of **10** (27 mg, 0.0590 mmol, 1.0 equiv.) in dichloromethane (1 mL). After 1 h, the resulting mixture was concentrated under reduced pressure. The resulting crude residue was dissolved in methanol (1 mL). Triethylamine (0.5 mL) was added and the mixture was heated to 50°C. After 2 h, the resulting mixture was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel: diam. 1.5 cm, ht. 12 cm; eluent: acetone : hexanes = 1 : 3 to 1 : 1) to afford secu'amamine E (**12**) (12 mg, 86% for 2 steps) as a white gum.

Experimental procedures for the synthesis of (+)-4-desmethoxysecuringine A (6)

secu'amamine E (**12**) → **6**

m-CPBA
K$_2$CO$_3$

CH$_2$Cl$_2$
0 °C to 23 °C

66%

3-Chloroperoxybenzoic acid (77%, 13 mg, 0.0561 mmol, 1.1 equiv.) was added to a solution of secu'amamine E (**12**) (12 mg, 0.0510 mmol, 1.0 equiv.) in dichloromethane (1.5 mL) at 0°C. Then, potassium carbonate (21 mg, 0.153 mmol, 3.0 equiv.) was added at 0°C and the resulting mixture was slowly warmed to 23°C. After 4 h, the reaction was quenched with brine (5 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layer was dried over anhydrous sodium sulfate. The resulting filtrate was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel: diam. 1.5 cm, ht. 12 cm; eluent: acetone : hexanes = 1 : 3) to afford **6** (8.5 mg, 66%) as a white solid.

Experimental procedures for the synthesis of (–)-*ent*-securinol A (19)

11 → *ent*-securinol A (**19**)

1. DBU
    THF, 23 °C

2. Et$_3$N
    MeOH, 50 °C

82% (2 steps)

1,8-Diazabicyclo[5.4.0]undec-7-ene (51 μL, 0.339 mmol, 5.0 equiv.) was added to a solution of **11** (31 mg, 0.0678 mmol, 1.0 equiv.) in dichloromethane (1 mL). After 1 h, the resulting mixture was concentrated under reduced pressure. The resulting crude residue was dissolved in methanol (1 mL). Triethylamine (0.5 mL) was added and the mixture was heated to 50°C. After 2 h, the resulting mixture was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel: diam. 1.5 cm, ht. 12 cm; eluent: acetone : hexanes = 1 : 3 to 1 : 1) to afford *ent*-securinol A (**19**) (13 mg, 82% for 2 steps) as a white gum.

Experimental procedures for the synthesis of (+)-4-desmethoxy-7-*epi*-securingine A (7)

ent-securinol A (**19**) → **7**

m-CPBA
K$_2$CO$_3$

CH$_2$Cl$_2$
0 °C to 23 °C

86%

3-Chloroperoxybenzoic acid (77%, 14 mg, 0.0608 mmol, 1.1 equiv.) was added to a solution of *ent*-securinol A (**19**) (13 mg, 0.0553 mmol, 1.0 equiv.) in dichloromethane (2 mL) at 0°C. Then, potassium carbonate (23 mg, 0.166 mmol, 3.0 equiv.) was added at 0°C and the resulting mixture was slowly warmed to 23°C. After 4 h, the reaction was quenched with brine (5 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layer was dried over anhydrous sodium sulfate. The resulting filtrate was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel: diam. 1.5 cm, ht. 16 cm; eluent: acetone : hexanes = 1 : 3) to afford **7** (12 mg, 86%) as a white solid.

Experimental procedures for the synthesis of (+)-menisdaurilide (15)

20 → **menisdaurilide (15)**

TBAF
AcOH

THF, 23 °C

95%
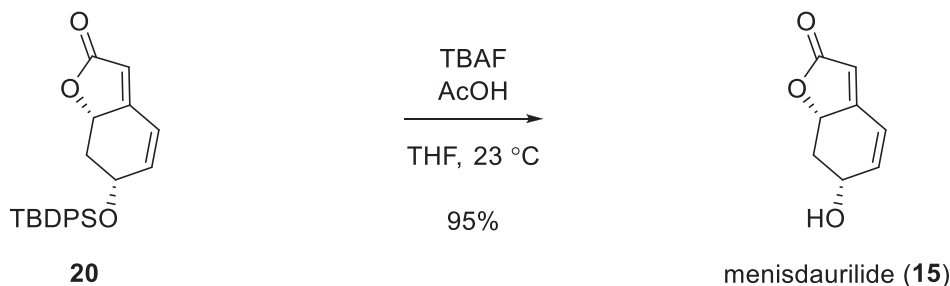
Acetic acid (0.21 mL, 3.58 mmol, 4.0 equiv.) and tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 3.58 mL, 3.58 mmol, 4.0 equiv.) were sequentially added to a solution of TBDPS-protected menisdaurilide[17] (**20**) (350 mg, 0.896 mmol, 1.0 equiv.) in tetrahydrofuran (18 mL) at 23°C. After 1.5 h, the reaction was quenched with ammonium chloride (saturated aqueous solution, 25 mL) and the aqueous layer was extracted with dichloromethane (10 × 40 mL) and the combined organic layer was dried over anhydrous sodium sulfate. The resulting filtrate was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel: diam. 2.5 cm, ht. 8 cm; eluent: ethyl acetate : hexanes = 2 : 1) to afford menisdaurilide (**15**) (130 mg, 95%) as a white solid.

Spectroscopic details

(+)-ε-Chloro butenolide 9

^{1}**H NMR** (400 MHz, CDCl$_3$, major rotamer): δ 7.76 (d, J = 7.5 Hz, 2H), 7.50 (t, J = 7.2 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.36 – 7.28 (m, 2H), 6.57 (dd, J = 9.9, 2.2 Hz, 1H), 6.17 (dd, J = 10.1, 2.8 Hz, 1H), 5.70 (s, 1H), 4.74 (ddd, J = 10.8, 5.5, 2.6 Hz, 1H), 4.39 – 4.33 (m, 1H), 4.32 – 4.21 (m, 2H), 4.18 (t, J = 6.9 Hz, 1H), 3.93 (dd, J = 14.5, 5.6 Hz, 1H), 3.14 (ddd, J = 14.0, 11.9, 4.9 Hz, 1H), 3.05 (dd, J = 13.0, 5.7 Hz, 1H), 2.11 (dd, J = 13.1, 11.1 Hz, 1H), 2.03 (td, J = 7.6, 3.7 Hz, 1H), 1.92 – 1.74 (m, 2H), 1.69 – 1.61 (m, 1H), 1.54 – 1.40 (m, 2H).

^{13}**C NMR** (101 MHz, CDCl$_3$, major rotamer): δ 171.8, 164.0, 156.4, 144.0, 143.8, 141.5, 141.5, 136.1, 128.0 (2), 127.3 (2), 125.2 (2), 122.9, 120.2 (2), 112.9, 88.7, 67.7, 53.2, 51.9, 47.2, 41.7, 40.8, 24.0, 23.6, 18.7.

HRMS (ESI): Calculated for C$_{28}$H$_{26}$NO$_4$Cl [M+Na]$^+$: 498.1443, found: 498.1449.

TLC (acetone : hexanes = 1 : 4) Rf: 0.32 (UV, KMnO$_4$).

$[\alpha]_D^{25}$: 18.1 (c 0.1, MeOH).

Note: ^{1}H-NMR spectrum shows two sets of signals, due to the presence of two rotamers in proportion 73:27. This assignation was corroborated with the same ^{1}H-NMR and EXSY experiments, where exchange signals between absorptions of the same proton but corresponding to different rotamers, were observed. This behaviour can be also observed in the ^{13}C-NMR spectrum.

ε-Hydroxy butenolide (–)-10

^{1}**H NMR** (400 MHz, CDCl$_3$, major rotamer): δ 7.76 (d, J = 7.4 Hz, 2H), 7.51 (t, J = 7.3 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.36 – 7.29 (m, 2H), 6.54 (dd, J = 10.0, 2.2 Hz, 1H), 6.19 (dt, J = 9.9, 1.6 Hz, 1H), 5.65 (s, 1H), 4.55 (dtd, J = 10.5, 5.4, 2.7 Hz, 1H), 4.35 (dd, J = 10.1, 6.5 Hz, 1H), 4.26 – 4.15 (m, 3H), 3.94 (dd, J = 14.1, 6.0 Hz, 1H), 3.16 (ddd, J = 13.7, 12.0, 4.8 Hz, 1H), 2.90 (dd, J = 12.4, 5.5 Hz, 1H), 2.26 (d, J = 7.2 Hz, 1H), 2.11 – 2.01 (m, 1H), 1.95 – 1.77 (m, 2H), 1.74 (dd, J = 12.4, 10.5 Hz, 1H), 1.69 – 1.59 (m, 1H), 1.54 – 1.41 (m, 2H).

^{13}**C NMR** (101 MHz, CDCl$_3$, major rotamer): δ 172.4, 165.5, 156.4, 144.0, 143.8, 141.5, 141.5, 139.3, 127.9 (2), 127.3 (2), 125.2, 125.2, 122.3, 120.2 (2), 112.0, 89.5, 67.7, 65.8, 53.5, 47.2, 41.4, 40.9, 24.1, 23.7, 18.8.

HRMS (ESI): Calculated for C$_{28}$H$_{27}$NO$_5$ [M+Na]$^+$: 480.1782, found: 480.1785.

TLC (acetone : hexanes = 1 : 1.5) Rf: 0.38 (UV, KMnO$_4$).

$[\alpha]_D^{25}$: –14.2 (c 0.1, MeOH).

Note: ^{1}H-NMR spectrum shows two sets of signals, due to the presence of two rotamers in proportion 76:24. This assignation was corroborated with the same ^{1}H-NMR and EXSY experiments, where exchange signals between absorptions of the same proton but corresponding to different rotamers, were observed. This behaviour can be also observed in the ^{13}C-NMR spectrum.

ε-Hydroxy butanolide (–)-11

^{1}**H NMR** (400 MHz, CDCl$_3$, major rotamer): δ 7.76 (d, J = 7.1 Hz, 2H), 7.52 (t, J = 8.2 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.36 – 7.30 (m, 2H), 6.56 (d, J = 9.8 Hz, 1H), 6.14 (ddd, J = 9.8, 4.7, 1.2 Hz, 1H), 5.64 (s, 1H), 4.68 – 4.57 (m, 2H), 4.42 – 4.31 (m, 1H), 4.26 – 4.17 (m, 2H), 3.95 (dd, J = 13.1, 6.4 Hz, 1H), 3.13 (ddd, J = 13.9, 12.0, 5.2 Hz, 1H), 2.66 (d, J = 14.1 Hz, 1H), 2.38 (d, J = 4.3 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.95 (dddd, J = 16.8, 9.9, 6.9, 3.3 Hz, 1H), 1.89 – 1.75 (m, 2H), 1.62 (ddt, J = 16.8, 11.3, 5.3 Hz, 1H), 1.50 (dq, J = 12.7, 6.4 Hz, 1H), 1.48 – 1.36 (m, 1H).

^{13}**C NMR** (101 MHz, CDCl$_3$, major rotamer): δ 172.6, 165.5, 156.6, 144.1, 143.9, 141.5, 141.5, 134.2, 127.9 (2), 127.3 (2), 125.2, 125.2, 123.4, 120.2 (2), 112.8, 88.6, 67.6, 64.6, 55.4, 47.3, 40.8, 37.3, 23.3 (2), 18.9.

HRMS (ESI): Calculated for $C_{28}H_{27}NO_5$ [M+Na]$^+$: 480.1782, found: 480.1790.

TLC (acetone : hexanes = 1 : 1.5) R*f*: 0.52 (UV, KMnO$_4$).

$[\alpha]_D^{25}$: –179.1 (c 0.1, MeOH).

Note: ^{1}H-NMR spectrum shows two sets of signals, due to the presence of two rotamers in proportion 70:30. This assignation was corroborated with the same ^{1}H-NMR and EXSY experiments, where exchange signals between absorptions of the same proton but corresponding to different rotamers, were observed. This behaviour can be also observed in the ^{13}C-NMR spectrum.

(–)-Secu'amamine E (12)

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.69 (s, 1H), 4.37 (dt, *J* = 8.9, 3.9 Hz, 1H), 2.97 (d, *J* = 18.3 Hz, 1H), 2.93 – 2.87 (m, 2H), 2.79 (dd, *J* = 18.5, 3.9 Hz, 1H), 2.76 – 2.66 (m, 3H), 2.08 (br s, 1H), 1.80 (dt, *J* = 13.7, 3.7 Hz, 1H), 1.58 – 1.52 (m, 2H), 1.52 – 1.43 (m, 1H), 1.45 (dd, *J* = 12.4, 5.0 Hz, 1H), 1.28 (qt, *J* = 11.8, 4.1 Hz, 1H), 0.85 (qd, *J* = 12.0, 4.0 Hz, 1H).

^{13}C NMR (151 MHz, CDCl$_3$): δ 174.3, 174.3, 111.6, 84.6, 65.4, 65.2, 59.1, 52.9, 41.0, 29.6, 26.8, 25.8, 24.1.

HRMS (ESI): Calculated for $C_{13}H_{17}NO_3$ [M+H]$^+$: 236.1282, found: 236.1286.

TLC (acetone : hexanes = 1 : 1.5) R*f*: 0.45 (KMnO$_4$).

$[\alpha]_D^{25}$: –68.3 (c 0.1, MeOH).

(+)-4-Desmethoxysecuringine A (6)

^{1}H NMR (400 MHz, CDCl$_3$): δ 6.10 (dd, *J* = 10.1, 2.8 Hz, 1H), 5.91 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.38 (dtd, *J* = 9.4, 4.7, 2.3 Hz, 1H), 3.41 (dt, *J* = 8.9, 3.3 Hz, 1H), 3.05 (d, *J* = 18.8 Hz, 1H), 2.73 (d, *J* = 18.8 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.41 (dd, *J* = 13.3, 5.0 Hz, 1H), 2.04 (dd, *J* = 11.5, 2.6 Hz, 1H), 1.92 – 1.84 (m, 1H), 1.87 (dd, *J* = 13.5, 9.1 Hz, 1H), 1.84 – 1.75 (m, 2H), 1.81 (d, *J* = 5.3 Hz, 1H), 1.69 – 1.57 (m, 2H), 1.21 (qt, *J* = 13.3, 4.4 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 174.5, 134.6, 127.1, 93.4, 80.7, 73.0, 64.3, 55.0, 42.3, 37.7, 24.8, 24.2, 23.2.

HRMS (ESI): Calculated for $C_{13}H_{17}NO_4$ [M+H]$^+$: 252.1231, found: 252.1237.

TLC (acetone : hexanes = 1 : 2) R*f*: 0.25 (KMnO$_4$).

$[\alpha]_D^{25}$: 179.2 (c 0.1, MeOH).

(–)-*ent*-Securinol A (19)

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.73 (t, *J* = 2.0 Hz, 1H), 4.19 (dt, *J* = 9.3, 2.3 Hz, 1H), 3.23 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.03 – 2.92 (m, 4H), 2.45 (dt, *J* = 18.7, 1.8 Hz, 1H), 2.37 (br s, 1H), 2.16 (dd, *J* = 13.3, 1.8 Hz, 1H), 1.98 (dd, *J* = 13.2, 9.1 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.61 – 1.52 (m, 2H), 1.46 – 1.32 (m, 2H), 0.89 (qd, *J* = 12.1, 4.5 Hz, 1H).

^{13}C NMR (151 MHz, CDCl$_3$): δ 174.1, 172.6, 112.6, 85.0, 70.2, 63.3, 59.3, 53.2, 41.5, 30.9, 26.5, 24.9, 23.2.

HRMS (ESI): Calculated for $C_{13}H_{17}NO_3$ [M+H]$^+$: 236.1282, found: 236.1287.

TLC (acetone : hexanes = 1 : 1.5) R*f*: 0.46 (KMnO$_4$).

$[\alpha]_D^{25}$: –56.1 (c 0.1, MeOH).

(+)-4-Desmethoxy-7-*epi*-securingine A (7)

^{1}H NMR (400 MHz, CDCl$_3$): δ 6.02 (dd, *J* = 10.5, 2.1 Hz, 1H), 5.92 (dd, *J* = 10.3, 2.2 Hz, 1H), 4.39 (ddq, *J* = 9.9, 5.1, 2.4 Hz, 1H), 3.42 (dt, *J* = 9.1, 3.4 Hz, 1H), 3.10 (d, *J* = 18.9 Hz, 1H), 2.56 (d, *J* = 18.9 Hz, 1H), 2.54 – 2.46 (m, 1H), 2.46 (dd, *J* = 13.9, 4.4 Hz, 1H), 2.16 (dd, *J* = 11.6, 2.6 Hz, 1H), 2.00 (d, *J* = 5.2 Hz, 1H), 1.88 (ddq, *J* = 13.2, 4.5, 2.3 Hz, 1H), 1.83 – 1.74 (m, 2H), 1.69 (dd, *J* = 13.6, 9.6 Hz, 1H), 1.64 – 1.51 (m, 2H), 1.23 (qt, *J* = 13.5, 4.3 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 174.7, 135.0, 127.2, 94.0, 80.8, 76.1, 63.8, 54.9, 42.8, 37.3, 24.6, 24.3, 23.2.

HRMS (ESI): Calculated for $C_{13}H_{17}NO_4$ [M+H]$^+$: 252.1231, found: 252.1238.

TLC (acetone : hexanes = 1 : 2) R*f*: 0.26 (KMnO$_4$).

$[\alpha]_D^{25}$: 123.5 (c 0.1, MeOH).

(+)-Menisdaurilide (15)

^{1}H NMR (500 MHz, CDCl$_3$): δ 6.58 (dd, *J* = 9.9, 2.5 Hz, 1H), 6.32 (dt, *J* = 9.9, 1.7 Hz, 1H), 5.83 (s, 1H), 4.88 (ddd, *J* = 13.3, 4.9, 1.9 Hz, 1H), 4.64 (ddt, *J* = 10.2, 5.1, 2.3 Hz, 1H), 2.95 (dtt, *J* = 11.3, 5.2, 1.2 Hz, 1H), 1.67 (dt, *J* = 13.3, 10.7 Hz, 1H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 173.4, 162.9, 143.5, 120.3, 111.9, 78.1, 77.5, 77.2, 77.0, 67.0, 40.2.

HRMS (ASAP): Calculated for $C_8H_8O_3$ [M–H]$^-$: 151.0400, found: 151.0401.

TLC (ethyl acetate : hexanes = 2 : 1) R*f*: 0.25 (UV, KMnO$_4$).

$[\alpha]_D^{25}$: 29.1 (c 0.5, MeOH). [Lit. 27.6 (c 0.6, MeOH)].[26]