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Total Synthesis of 4α-Hydroxyallosecurinine and Securingine F, Securinega Alkaloids with a C4-Hydroxy Handle for Biofunctional Derivatizations

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This work is dedicated to Professor Hee-Yoon Lee (1957–2023) in memory of his scientific contributions to the field of total synthesis.

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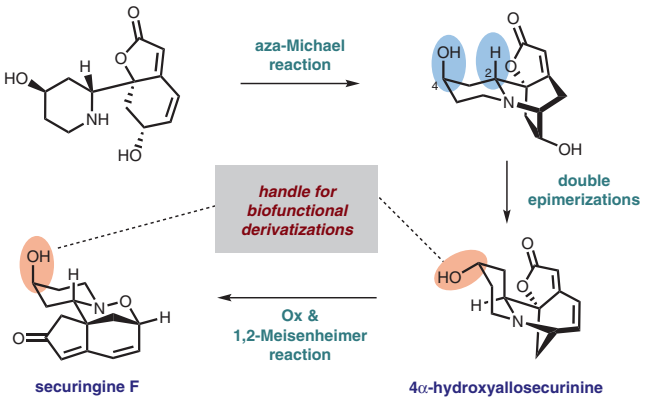

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Abstract We describe the first total synthesis of the C4-hydroxylated securinega alkaloids 4α-hydroxyallosecurinine and securingine F. The synthetic route features an Ellman's light-mediated hydrogen-atom-transfer-based epimerization reaction that effectively sets the desired configuration at the C2 position. Simultaneous skeletal rearrangement from neosecurinane to securinane frameworks and stereochemical reversal at the C4 site was achieved under Mitsunobu reaction conditions. The C4-hydroxy group is envisioned to serve as a handle for potential biofunctional derivatizations.

Key words total synthesis, securinega alkaloids, biofunctional derivatizations, hydroxyallosecurinine, securingine F

Natural products have played a vital role in the development of new drugs.[1] Among the 185 cancer-related small-molecule drugs approved from 1981 to 2019, 62 (33.5%) were natural products or natural-product derivatives and 58 (31.4%) were synthetic drugs with natural-product pharmacophores or natural-product-mimicking synthetic drugs.[2] Natural-product-based drug development can undoubtedly benefit from the identification of the targets. In recent years, studies that described the syntheses of complex natural products and of associated probes for the identification of their targets have been reported.[3–6] In all these examples, the presence of a functional handle that permits anchoring of the target-signal-enhancing moiety was essential (Scheme 1A). Notably, the Dai group used a hydroxy group as a functional handle for the synthesis of alkyne-based[5] and azide-based[3] natural-product chemoproteomics probes.

Antibody–drug conjugates (ADCs) represent an emerging class of drugs with a wider therapeutic index than classical chemotherapeutic agents, due to their selective drug delivery to antigen-expressing tumor cells. Since the first approval of an ADC drug, Mylotarg (gemtuzumab ozogamicin), by the US Food and Drug Administration (FDA), 14 ADCs have received market approval worldwide.[7] Importantly, the payloads of all of these drugs have their origins in natural-product structures.[8] Hence, the presence of a functional handle in the payload is essential to conjugate the linker that connects the warhead and the antibody (Scheme 1A). On the other hand, natural products without functional handles would be relatively more difficult to use in the aforementioned bioapplications such as target identification and ADC (Scheme 1A).

Securinega alkaloids have fascinated the chemical community for over six decades because of their promising biological activities and intriguing structures.[9–11] They show a potent antitumor activity that is based on cytotoxicity, differentiation-induction activity, and the reversal of multidrug-resistance activity.[12] Securinega alkaloids also exhibit nervous-system-related and cardiovascular-system-related activities.[12] Even though a few preliminary mechanistic studies regarding the bioactivities of these alkaloids have been reported, the exact targets for the majority of these bioactivities have yet to be identified. Notably, Chen and co-workers reported that securinine derivatives effectively inhibit DNA topoisomerase I (Topo I),[13,14] the target of the FDA-approved ADC drug Enhertu (trastuzumab deruxtecan).[15]

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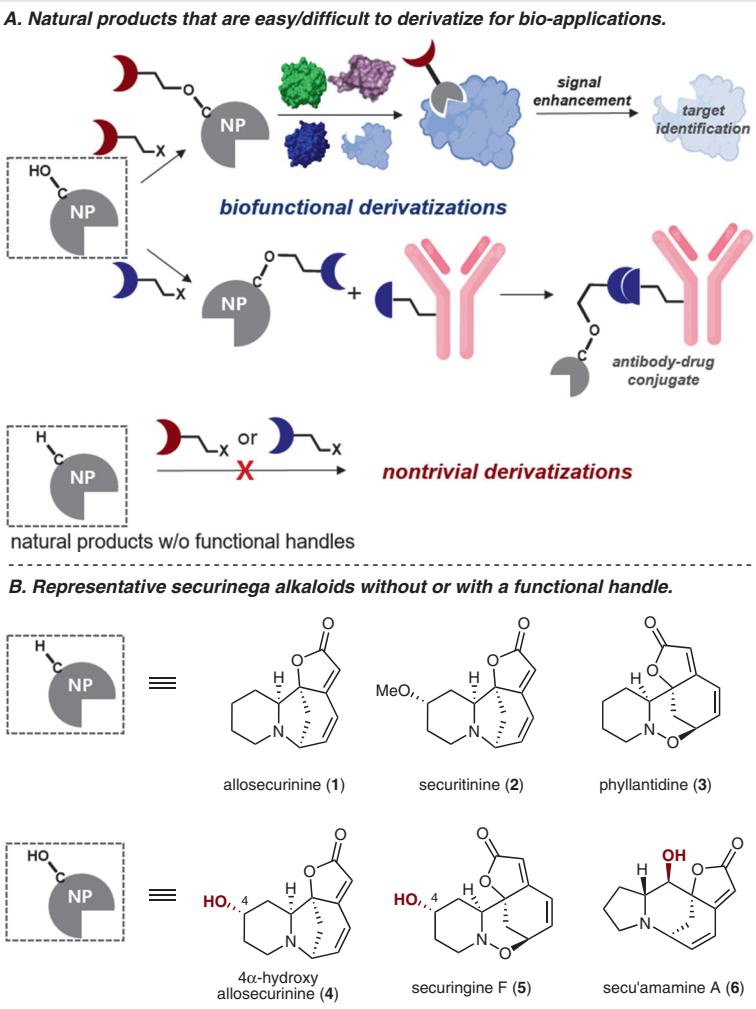

Scheme 1 Importance of securinega alkaloids with a handle for biofunctional derivatizations

From a structural perspective, basic monomeric securinega alkaloids are characterized by a fused tetracyclic core with a conjugated ester moiety and a piperidine heterocycle. It is noteworthy that most securinega alkaloids lack a functional handle for biofunctional derivatizations, considering that altering the electrophilic unsaturated γ-butyrolactone moiety is not desirable because it may interact with the nucleophilic moiety of the target (Scheme 1B). Under these circumstances, isolations of securinega alkaloids with a hydroxy group, such as 4α-hydroxyallosecurinine (**4**),[16] securingine F (**5**),[17] or secu'amamine A (**6**)[18–22] are notable. 4α-Hydroxyallosecurinine (**4**) and securingine F (**5**) are especially interesting entries, as their hydroxy group is located remotely from both the unsaturated γ-butyrolactone and the N1 moieties, two probable sites for biological activities of the natural product. Hence, building on our group's successful synthesis of C4-methoxylated high-oxidation-state securinega alkaloids,[23] we decided to attempt syntheses of 4α-hydroxyallosecurinine (**4**) and securingine F (**5**), structurally unique high-oxidation-state securinega alkaloids with a C4-hydroxy group as a potential handle for biofunctional derivatizations.

Our retrosynthetic analysis of securingine F (**5**) and 4α-hydroxyallosecurinine (**4**) is shown in Scheme 2. Securingine F (**5**) could be obtained from 4α-hydroxyallosecurinine (**4**) through N-oxidation and a subsequent 1,2-Meisenheimer rearrangement. We planned to access 4α-hydroxyallosecurinine (**4**) by a 1,2-amine shift and C4-epimerization of diol **8**. Diol **8** could be obtained from compound **9** through a hydrogen-atom-transfer (HAT)-mediated C2-epimerization. The tetracyclic framework of **9** would result from an intramolecular 1,6-aza-Michael addition of the known compound **10**.[23]

Our synthesis commenced with a Michael addition-based stereoselective union of enone **11** and menisdaurilide derivative **12**, and subsequent transformations to yield the tricyclic compound **10** by following our previously reported protocol (Scheme 3).[23] The *tert*-butyl(diphe-

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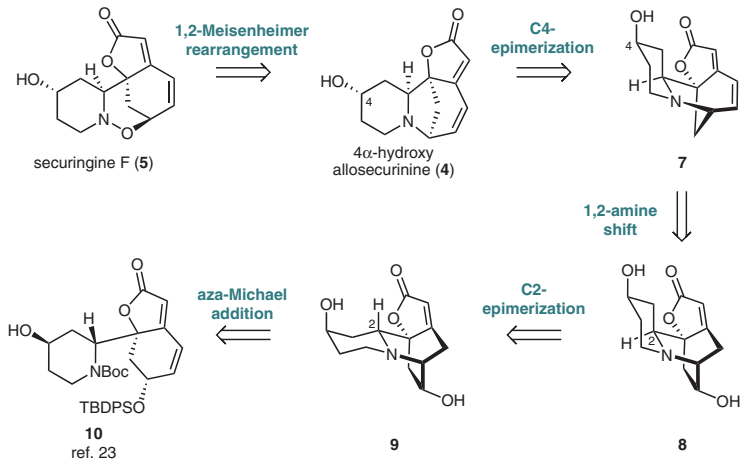
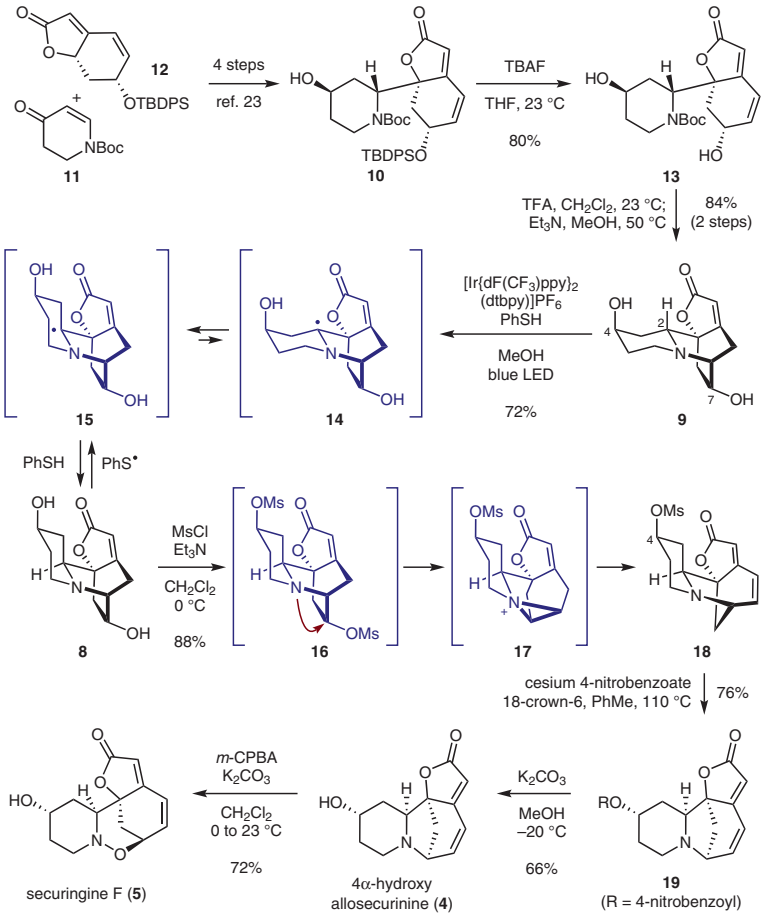


Scheme 2 Retrosynthetic analysis of 4α-hydroxyallosecurinine (**4**) and securingine F (**5**)



Scheme 3 The first-generation total synthesis of 4α-hydroxyallosecurinine (**4**) and securingine F (**5**)

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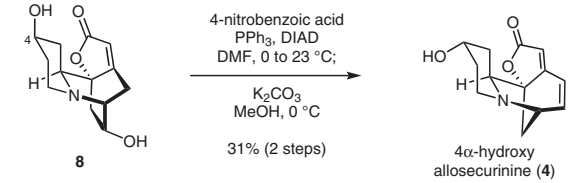
nyl)silyl moiety in compound **10** was removed by reaction with TBAF to yield the allylic alcohol **13** in 80% yield. A TFA-mediated Boc-deprotection of carbamate **13** and subsequent treatment of the resulting amine intermediate with triethylamine in methanol resulted in an intramolecular aza-1,6-conjugate addition to afford tetracyclic compound **9** with a neosecurinane framework in 84% yield over two steps.[24]

With robust synthetic access to **9**, we faced the challenge of epimerizing the C2 position of the compound. In 2020, Ellman and co-workers reported a light-induced HAT-mediated epimerization of piperidine.[25] Our group used this transformation in the total synthesis of 4-*epi*-phyllanthine.[23] We envisioned that the radical-based epimerization might also be applicable to the C2-selective epimerization of **9**. To our delight, when compound **9** was irradiated with blue LEDs in the presence of 1 mol% of [Ir{dF(CF_3)ppy}$_2$(dtbpy)]PF_6 [dF(CF_3)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine] and benzenethiol for 13 hours, the C2-epimerized product **8** was obtained in 72% yield. The reaction mechanism involves the catalytic generation of a thiol radical that reversibly abstracts the hydrogen atom at the C2 position to set the thermodynamic equilibrium between compounds **8** and **9**. Product **8**, with the hydroxy group in the equatorial position, would be thermodynamically more stable than **9**, consistent with the A-value of the hydroxy group in methanol (0.9 kcal/mol). It is worthwhile noting that prolonged exposure of compound **9** to the aforementioned reaction conditions initiated an epimerization at the C7 position.

Treatment of diol **8** with excess mesyl chloride (4 equiv) and triethylamine (8 equiv) afforded the dimesylated intermediate **16**, which underwent spontaneous intramolecular N-alkylation to give the aziridinium ion intermediate **17**. Subsequent E1cB elimination of intermediate **17** yielded the 1,2-amine-shifted product **18** in 88% yield.[24] When the mesylate derivative **18** was treated with cesium 4-nitrobenzoate, the S_N2-reaction-mediated O-alkylated product **18** was obtained in 76% yield. Final methanolysis of the nitrobenzoate moiety in **19** produced the first synthetic sample of 4α-hydroxyallosecurinine (**4**) in 66% yield. Spectroscopic data for the synthetic 4α-hydroxyallosecurinine (**4**) were consistent with those of the natural sample,[16] confirming its structure.[26,27] Furthermore, treatment of 4α-hydroxyallosecurinine (**4**) with *m*CPBA and potassium carbonate produced securingine F (**5**) in 72% yield through a 1,2-Meisenheimer rearrangement.[28]

After completing the first-generation total synthesis of 4α-hydroxyallosecurinine (**4**) and securingine F(**5**), we envisioned further streamlining of the synthetic route. We postulated that both the 1,2-amine shift and the stereochemical inversion at the C4 site would be possible under Mitsunobu reaction conditions. Pleasingly, when diol **8** was allowed to react with 4-nitrobenzoic acid, triphenylphosphine, and diisopropyl azodicarboxylate (DIAD), with subsequent treatment by potassium carbonate in methanol, 4α-hydroxyallosecurinine (**4**) was obtained in 31% yield over the two steps (Scheme 4).



Scheme 4 Simultaneous C4-epimerization and 1,2-amine shift of diol **8** under Mitsunobu reaction conditions

To conclude, we have successfully achieved the first total synthesis of 4α-hydroxyallosecurinine (**4**) and securingine F (**5**). Importantly, our synthetic route features complete stereoflexibility and stereocontrollability at both the C2 and C4 positions of the securinega framework and, therefore, various stereochemical congeners should be synthetically accessible. Furthermore, we envisioned coupling the newly developed strategy for the introduction of the hydroxy group at the C4 position of the securinega skeleton with our previously established synthetic chemistry toward various high-order and high-oxidation-state securinega alkaloids.[11] This would permit the synthesis of various complex high-order and high-oxidation-state securinega alkaloids with a C4-hydroxy handle. Those congeners could be subjected to biofunctional derivatizations and biological studies. Those will be the subject of our forthcoming reports.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2047-9680.

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(28) **(–)-Securingine F (5)**
*m*CPBA (77%, 3.6 mg, 0.0160 mmol, 1.1 equiv) was added to a solution of 4α-hydroxyallosecurinine (**4**) (3.4 mg, 0.0146 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at 0 °C. After 5 min, K_2CO_3 (6.0 mg, 0.0437 mmol, 3.0 equiv) was added, 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 CH_2Cl_2 (3 × 10 mL) and the combined organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography [silica gel, CH_2Cl_2–acetone (6:1)] to give a white amorphous solid; yield: 2.6 mg (72%); R_f = 0.44 (UV, $KMnO_4$); $[\alpha]_D^{25}$ –250.6 (*c* 0.1, MeOH) [Lit.[4] –167.1 (*c* 0.1, MeOH)].
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (d, *J* = 9.4 Hz, 1 H), 6.29 (dd, *J* = 9.4, 5.8 Hz, 1 H), 5.83 (s, 1 H), 4.73 (dt, *J* = 5.8, 2.9 Hz, 1 H), 4.08–4.02 (m, 1 H), 3.30 (dd, *J* = 12.0, 2.6 Hz, 1 H), 3.07–2.95 (m, 2 H), 2.54 (dd, *J* = 11.5, 3.4 Hz, 1 H), 2.03 (dd, *J* = 11.4, 2.4 Hz, 1 H), 1.83 (dd, *J* = 13.7, 2.7 Hz, 1 H), 1.80–1.74 (m, 2 H), 1.18 (ddd, *J* = 14.0, 12.1, 2.7 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.1, 164.4, 134.6, 126.6, 113.6, 82.7, 71.2, 65.1, 63.6, 50.0, 40.8, 32.0, 31.3. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{15}NNaO_4$: 272.0893; found: 272.0894.

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