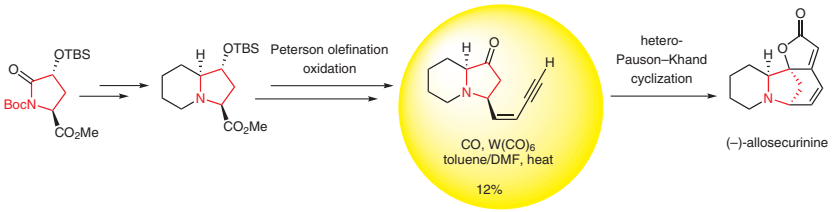
Synthesis E. Chirkin et al. Paper

Tungsten-Promoted Hetero-Pauson–Khand Cycloaddition: Application to the Total Synthesis of (–)-Allosecurinine

Egor Chirkin[1]
Chouaha Bouzidi
François-Hugues Porée*

Laboratoire de Pharmacognosie UMR CNRS 8638, Faculté de Pharmacie, Université Paris Descartes, 4 Avenue de l'Observatoire, 75006 Paris, France
francois-hugues.poree@parisdescartes.fr



Received: 06.12.2018
Accepted after revision: 17.12.2018
Published online: 18.02.2019
DOI: 10.1055/s-0037-1612063; Art ID: ss-2018-t0703-op

Abstract Herein, we report a concise enantioselective synthesis of (–)-allosecurinine, a tetracyclic Securinega alkaloid featuring an α,β-unsaturated γ-lactone moiety. Starting from inexpensive and readily available *trans*-L-hydroxyproline, our strategy entails a rare late-stage [2+2+1]-hetero-Pauson–Khand cycloaddition between a ketone and an alkyne as the key complexity-generating step to rapidly install the CD-ring system. The reported $W(CO)_6$-promoted intramolecular cyclization provides the first example of a tungsten-mediated hetero-Pauson–Khand reaction. This approach to the strained bicyclic CD motif present in allosecurinine provides some insights into the boundaries of this potentially powerful methodology that might be further extended to other butenolide-containing natural products.

Key words alkaloids, total synthesis, tungsten, cyclization, natural products

Securinega alkaloids constitute a unique class of plant-derived alkaloids isolated from *Securinega* (= *Flueggea*), *Phyllanthus*, *Margaritaria*, and *Breynia* genera, of the Phyllanthaceae family.[2] Since the isolation of the first congener securinine (**1**), interest in this series culminated in the isolation of 80 compounds. Characteristic of this group is the occurrence of a compact tetracyclic backbone divided into four subgroups: securinane, neosecurinane, norsecurinane, and neonorsecurinane (Figure 1). In addition to this feature, it should be noted that almost all the stereoisomer combinations are naturally occurring, as recently reported by Yue for the neosecurinane group.[3] Therefore, these alkaloids represent appealing targets for total synthesis, and several original routes have been developed.[4] In addition, this series represents a good example of the helpful assistance of total synthesis to support the biogenesis hypothesis.[5] Besides, these alkaloids display promising biological activities. Securinine (**1**), the most abundant derivative, was first identified as a $GABA_A$ antagonist and used as a CNS agent.[6] Securinine (**1**) was shown to promote the differentiation of HL60 leukemic cells *in vitro* and demonstrated an *in vivo* activity in mouse xenograft experiments.[7] These biological activities make securinine (**1**) and its congeners a compelling starting point for the development of a medicinal chemistry program. Furthermore, systematic structure–activity relationship (SAR) studies have not yet been reported for this alkaloid family, and only a very limited set of analogues produced by semisynthetic modifications is available.[8] In addition to antileukemic activity, norsecurinine (**2**) and its analogues were reported to inhibit myeloperoxidase, an enzyme involved in immune inflammatory disorder.[9] The naturally occurring oligomers of norsecurinine (**2**) were also shown to exhibit anti-HIV activity.[10]

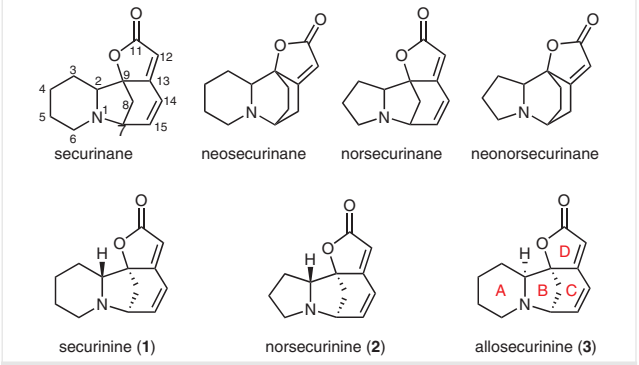


Figure 1 Structural diversity of Securinega alkaloids

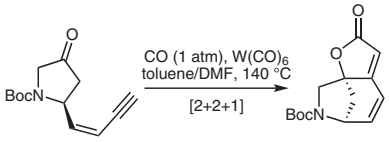
Within this context, a concise and flexible synthetic access to Securinega alkaloids is of general interest. The daunting construction of the critical butenolide-containing CD moiety gave rise in the past years to very creative synthetic solutions; however, most of them consisted of lengthy reaction sequences and thus did not lend them-

selves for the preparation of analogues for SAR studies.[5a,11] We recently proposed an efficient entry to this series with the use of a hetero-Pauson–Khand (HPK) strategy to construct the BCD core of the securinane/neosecurinane groups on a model compound.[12] Herein, we report our efforts to implement this cyclocarbonylation reaction to the synthesis of the securinane skeleton through the total synthesis of allosecurinine (**3**), the C2-epimer of securinine (**1**).

At the onset of our investigations, we faced the challenge to prove the overall viability of the HPK strategy toward the securinega alkaloids. To the best of our knowledge, the only attempt to implement the HPK strategy in this alkaloid family has been made by the group of Rovis in their efforts toward secu'amamine A.[13] However, this attempt met with failure, since the prepared highly functionalized substrate did not undergo the planned HPK cycloaddition. The advances made over the last few years in the HPK methodology led to the introduction of novel, more powerful transition-metal catalysts and promoters. This consideration prompted us to reinvestigate the application of the HPK strategy to the synthesis of securinega alkaloids. Of note, success in the application of an oxa-hetero-Pauson–Khand reaction (oxa-HPK)[14] would provide a well-suited and elegant synthetic solution, enabling the collective synthesis of securinega alkaloids and, importantly, designed analogues thereof. Based on our initial report on the construction of the BCD core of the securinane / norsecurinane core, we decided to investigate the capacity of other metal–carbonyl promoters to trigger the critical oxa-HPK event. One of our goals is to develop a *simple procedure* using an easy-to-handle metal complex. For this reason, we reported an all-together procedure, which was successfully applied by Tao et al.[14a] During the course of our investigations of other metal–carbonyl-containing complexes, $W(CO)_6$ was identified as a promising candidate for this reaction (Table 1).

The $W(CO)_6$ complex is a white, air-stable, and easy-to-handle solid. Using our procedure, we were delighted to observe the cyclization in only 30 minutes in 30% yield (Table 1, entry 1). This result was very encouraging, even though the yield was moderate. Interestingly, the same result was obtained with a charge of 1.1 equivalents of promoter after one hour (entry 2). Also, the reaction proceeded without a CO atmosphere in a low yield (12%, entry 3). At this stage, we were not able to improve this yield, and further investigations should be carried out, in particular on the use of CO under pressure. Nevertheless, these results constitute the first example of the use of the $W(CO)_6$ complex in the HPK reaction. With this encouraging result in hand, we next turned our efforts to illustrate the application of this procedure to the synthesis of allosecurinine (**3**).

Table 1 Construction of the BCD Core Using the $W(CO)_6$ Complex[a]

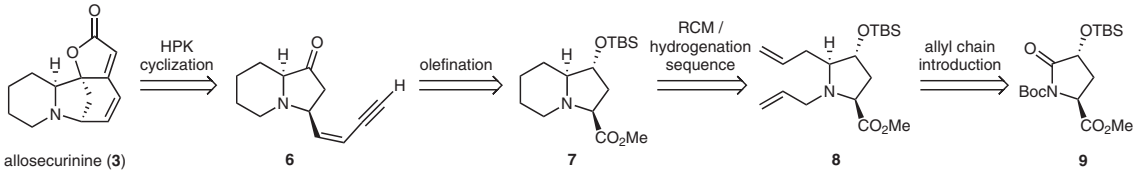


4 5

Entry	Time (h)	Yield (%)[b]
1	0.5	30
2[c]	1	29
3[d]	2	12

[a] Reaction conditions: **4** (0.33 mmol, 1 equiv), CO (initially 1 atm; pressure not assessed during reaction), $W(CO)_6$ (2.5 equiv), toluene/DMF (1:0.6 ratio; 1.2 mL/0.7 mL), 140 °C, sealed vial
[b] Isolated yields.
[c] $W(CO)_6$ (1.1 equiv) was used.
[d] The reaction was carried out under argon.

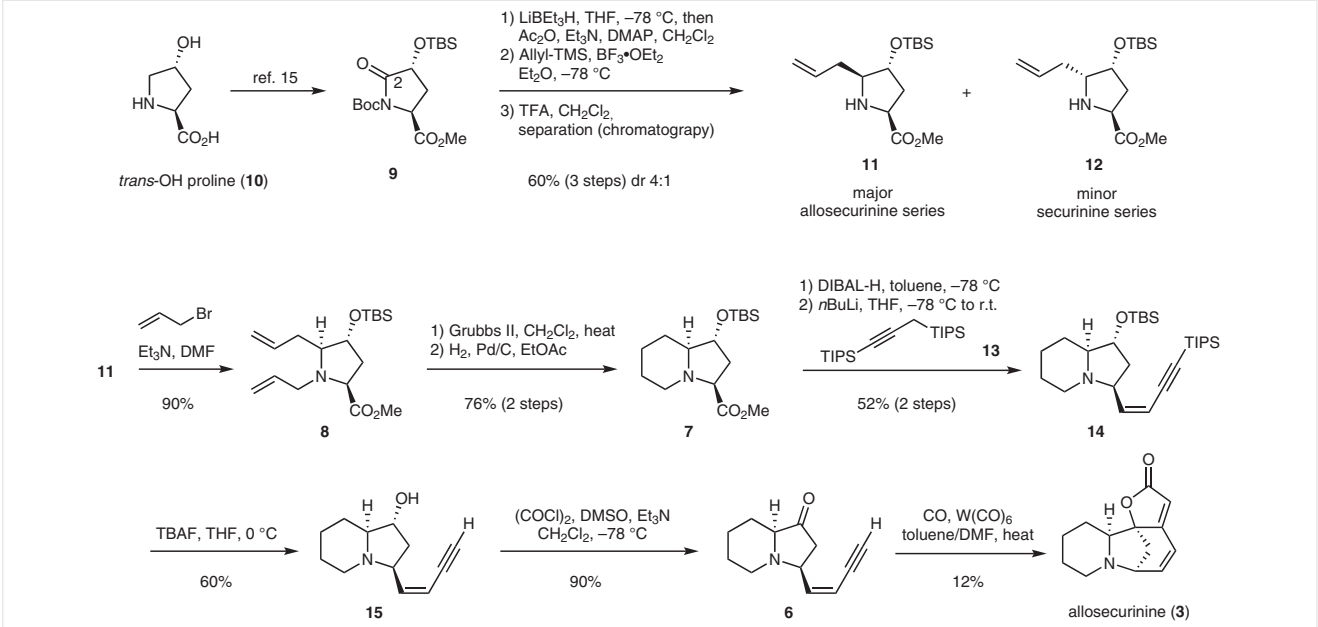
We focused on the securinane skeleton by investigating allosecurinine (**3**). The retrosynthetic plan is depicted in Scheme 1. The key HPK cyclization was envisaged as the last step of the synthesis of the bicyclic compound **6** featuring both a ketone and a *Z*-enyne function. Installation of the *Z*-enyne moiety could be envisaged to occur via a stereoselective olefination reaction following either a modified Julia–Kocienski or a Peterson approach on the in situ generated aldehyde derived from ester **7**. After removal of the TBS protecting group, oxidation of the secondary alcohol would give access to the corresponding ketone. Indolizidine **7** corresponding to the AB motif of the securinane skeleton could be prepared from bis-allyl compound **8** via an efficient RCM/hydrogenation sequence. The latter could derive from known oxo compound **9** after introduction of an allyl chain at the C2 and the nitrogen positions. To resume, the proposed strategy consists of the elaboration of the A ring from a B ring precursor and further one-step construction of the CD motif.



Scheme 1 Retrosynthetic analysis

During synthesis, compound **9** was prepared on a multigram scale from commercial L-OH proline **10** according to known procedures (Scheme 2).[15] According to Thadani, partial reduction of the C4-carbonyl by $LiBEt_3H$, followed by Ac_2O trapping furnished a mixture of acetates, which was treated with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ to yield an inseparable mixture of diastereomeric allyl compounds in overall good yields (85%).[15b] Boc removal by action of trifluoroacetic acid enabled separation of the diastereomers on silica gel, furnishing the 4*R*-compound **11** as the major one (60% over 3 steps, dr 4:1). Surprisingly, this result contrasted with the report of Thadani, giving the 4*S*-stereoisomer **12** as the major one.[15b] However, in our case, the observed stereochemistry is in favor of a steric control of the OTBS group during the attack of the in situ generated iminium by the allyltrimethylsilane agent and corresponds to the allosecurinine series.[16] The next sequence of the synthesis consisted of the construction of ring A. For this purpose, an allyl chain was introduced on the nitrogen atom to give the bis-allyl derivative **8** (90% yield), which was engaged in a Grubbs-II-catalyzed RCM cyclization reaction followed by Pd/C hydrogenation to furnish indolizidine **7** in 76% yield over the two steps.[17] Of note, during the metathesis event some epimerization at the C2-position was observed. At this stage, installation of the *Z*-enyne motif was considered. The Julia–Kocienski procedure which was successfully applied in the model study[12] gave disappointing results with the aldehyde derived from ester **7**. The yields were low, not constant, and purification of the reaction product from the residual sulfone proved to be difficult. Conversely, Peterson olefination in the presence of alkyne **13** offered an interesting alternative.[18] The overall yield and reproducibility were better and the expected *Z*-compound **14** was isolated in 52% yield. Then, the silyl groups were removed by action of TBAF at 0 °C and direct purification by chromatography without workup allowed isolation of alcohol **15** in 60% yield. Of note, the compound is very polar on normal-phase silica gel. Finally, a Swern oxidation was carried out to furnish ketone **6**, the precursor of the HPK cyclization. As previously reported, we followed the 'all together' procedure by mixing the substrate and the $W(CO)_6$ complex in a toluene/DMF mixture under a CO atmosphere at 140 °C for 0.5 h. To our delight, allosecurinine (**3**) was isolated after chromatography, albeit in low yield (12%).[19] When the $Mo(CO)_6$ complex was used as promotor, the same result was obtained (14%). However, this result demonstrates the viability of this strategy to access the securinane skeleton and its analogues. Efforts will next be on extending the scope of this cyclocarbonylation, in particular with regard to the impact of CO pressure on the outcome of the reaction.

In summary, our efforts to develop a concise synthetic route to the securinane skeleton of the Securinega alkaloids via a hetero-Pauson–Khand cyclocarbonylation and its application in the synthesis of allosecurinine (**3**) are reported. Despite a low yield, the present work demonstrates the usefulness of this reaction in total synthesis, in particular the capacity to generate a high degree of structural complexity. We identified hexacarbonyltungsten [$W(CO)_6$] as an unprecedented promoter of this annulation. Importantly, the reaction conditions did not require the use of air-unstable,



Scheme 2 Synthesis of allosecurinine (**3**)

preformed metal-containing complexes. Further theoretical and experimental work is needed to improve the overall yield and scope of this reaction.

All reactions were carried out under argon or nitrogen atmosphere with anhydrous solvents under anhydrous conditions, unless otherwise stated. Commercially available reagents were used without further purification, unless otherwise stated. Isolated yields are given, unless otherwise noted. NMR spectra were recorded on Bruker AC300 (300 MHz) and Bruker Avance III HD (400 MHz) instruments and processed with TopSpin Bruker software. NMR spectra were calibrated using the residual peaks of deuterated solvents as internal reference ($CDCl_3$: ^1H, 7.26; ^{13}C 77.0 ppm). IR spectra were recorded on a Perkin Elmer 60 FT-IR instrument; only selected absorbances are reported. High-resolution mass spectra were recorded in the UMR 8638 MS core facility using a Waters ZQ 2000 ESI spectrometer. Optical rotations were measured using a Perkin Elmer 314 polarimeter and concentration are reported in mg/mL.

Methyl (2*S*,4*R*,5*S*)-5-Allyl-4-(*tert*-butyldimethylsiloxy)pyrrolidine-2-carboxylate (11)

Step 1: Superhydride Reduction and Acetate Formation: To a solution of oxo compound **9**[15] (6.07 g, 16.2 mmol) in anhyd THF (30 mL) at –78 °C was added 1 M $LiBEt_3H$ in THF (17 mL, 17.01 mmol, 1.05 equiv) over 5 min. The reaction mixture was stirred for 1 h at –78 °C, and then quenched with sat. aq $NaHCO_3$ (15 mL). H_2O_2 (2 drops) was added and the resulting mixture was allowed to warm to r.t. All the volatiles were removed in vacuo. CH_2Cl_2 (30 mL) was added, followed by brine. After separation, the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The pale yellow oil was dissolved in CH_2Cl_2 (50 mL) and Et_3N (3.3 mL, 24.3 mmol, 1.5 equiv), Ac_2O (2.3 mL, 24.3 mmol, 1.5 equiv), and cat. DMAP were successively added. The mixture was stirred at r.t. overnight. Sat. aq $NaHCO_3$ was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a pad of silica (cyclohexane/EtOAc 8:2) to afford the corresponding acetates (6.75 g), which were used without further purification in the next step.

Step 2: Allyltrimethylsilane Addition: To a solution of the acetates (6.75 g) in anhyd Et_2O (100 mL) at –78 °C was added $BF_3{\cdot}OEt_2$ (2.5 mL, 20.2 mmol, 1.25 equiv) and allyltrimethylsilane (11.8 mL, 72.9 mmol, 4.5 equiv). The reaction mixture was stirred for 15 min at –78 °C and then allowed to warm to r.t. over 1 h, after which it was stirred a further 2 h at r.t. Sat. aq $NaHCO_3$ was added. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was filtered through a pad of silica (cyclohexane/EtOAc 9:1) to afford the corresponding allyl compounds as a pale yellow oil (5.5 g, 85%). This material was used without further purification in the next step.

Step 3: Boc Removal: To a solution of the allyl compounds (5.5 g, 13.8 mmol) in CH_2Cl_2 (100 mL) at 0 °C was slowly added TFA (10.5 mL, 138 mmol, 10 equiv). The reaction mixture was stirred at r.t. for 10 h. Sat. aq $NaHCO_3$ was carefully and slowly added at 0 °C. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, cyclohexane/EtOAc) to afford **11**.

Yield: 2.92. g (9.72 mmol, 70%; 60% from **9**); yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.85–5.76 (m, 1 H), 5.13–5.05 (m, 2 H), 3.93 (t, *J* = 13.0 Hz, 1 H), 3.88 (q, *J* = 5.4 Hz, 1 H), 3.71 (s, 3 H), 2.98–2.94 (m, 1 H), 2.35–2.28 (m, 1 H), 2.16–1.97 (m, 3 H), 0.86 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 135.2, 117.2, 76.0, 68.1, 57.9, 52.0, 38.8, 38.2, 25.8, 17.9, –4.5.

The analytical data matched well with those in the literature.[15]

Methyl (2*S*,4*R*,5*S*)-1,5-Diallyl-4-(*tert*-butyldimethylsiloxy)pyrrolidine-2-carboxylate (8)

To a solution of **11** (2.37 g, 7.89 mmol) in DMF (25 mL) at r.t. was added Et_3N (2.66 mL, 19.75 mmol, 2.5 equiv) and freshly distilled allyl bromide (0.98 mL, 11.83 mmol, 1.5 equiv). The resulting mixture was stirred for 16 h at r.t. Et_2O was then added and the organic layer was washed with sat. aq $NaHCO_3$. The layers were separated and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by chromatography (silica gel, cyclohexane/EtOAc 9:1).

Yield: 2.41 g (7.10 mmol, 90%); $[\alpha]_D^{20}$ –255 (*c* 2.5, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.76 (m, 2 H), 5.11–4.95 (m, 4 H), 3.96–3.92 (m, 1 H), 3.62 (s, OCH_3), 3.60–3.54 (m, 1 H), 3.35–3.23 (m, 2 H), 2.69–2.66 (m, 1 H), 2.26–2.19 (m, 1 H), 2.10–2.03 (m, 1 H), 2.00–1.93 (m, 1 H), 1.87–1.82 (m, 1 H), 0.82 (S, 9 H), –0.01 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 135.8, 135.0, 117.4, 116.5, 74.6, 71.4, 63.7, 57.0, 51.7, 38.4, 38.0, 25.8, 17.8, –4.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{33}NO_3SiNa$: 362.2127; found: 362.2139.

The analytical data matched well with those in the literature.[15]

Methyl (1*R*,3*S*,8a*S*)-1-(*tert*-Butyldimethylsiloxy)octahydroindolizine-3-carboxylate (7)

Step 1: RCM Cyclization: A round-bottom flask equipped with a condenser was charged with the Grubbs II catalyst (119 mg, 0.14 mmol, 0.05 equiv) and purged (3×) with an argon/vacuum cycle. Then, a solution of the above bis-allylpyrrolidine-2-carboxylate **8** (951 mg, 2.8 mmol) in anhyd CH_2Cl_2 (35 mL) was added and the red solution was refluxed for 4 h. A second charge of Grubbs II catalyst (50 mg) was added and reflux was maintained for an additional 4 h (total 8 h). The reaction mixture was cooled to r.t. and the solvent was removed in vacuo. The crude material was purified by flash chromatography (silica gel, cyclohexane/EtOAc 9:1 to 8:2); this afforded the corresponding indolizine.

Yield: 698 mg (2.24 mmol, 80%); yellowish oil; $[\alpha]_D^{20}$ –129 (*c* 5, $CHCl_3$).

IR (film): 2952, 2856, 1747, 1251, 1129, 1092, 834, 774 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.73–5.70 (m, 1 H), 5.64–5.60 (m, 1 H), 3.96–3.91 (m, 1 H), 3.71 (s, 3 H, OCH_3), 3.60–3.55 (m, 1 H), 3.23 (dd, *J* = 7.7 Hz, 9.5 Hz, 1 H), 2.82–2.77 (m, 1 H), 2.33–2.25 (m, 3 H), 2.14–2.09 (m, 1 H), 1.95–1.88 (m, 1 H), 0.86 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 124.7, 124.5, 75.8, 66.3, 65.4, 52.3, 52.0, 36.8, 30.2, 25.8, 18.0, –4.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{29}NO_3SiNa$: 334.1814; found: 334.1811.

Step 2: Hydrogenation: A round-bottom flask was charged with a solution of the above indolizine (1.403 g, 4.5 mmol) in EtOAc (50 mL) and purged with H_2. Then, Pd/C (Degussa-type, reference E105CA/W;

48 mg, 0.45 mmol, 10 mol%) was added and the resulting suspension was stirred overnight under a H_2 atmosphere. The mixture was filtered through a pad of silica and concentrated in vacuo to afford **7**.

Yield: 1.34 g (4.27 mmol, 95%); clean yellowish oil; $[\alpha]_D^{20}$ –90 (*c* 14, $CHCl_3$).

IR (film): 2930, 2855, 1752, 1255, 1196, 1088, 835, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.87 (q, *J* = 7.5 Hz, 1 H), 3.68 (s, 3 H), 3.12 (dd, *J* = 7.5 Hz, 9.4 Hz, 2 H), 2.21–2.14 (m, 1 H), 1.96–1.74 (m, 5 H), 1.58–1.49 (m, 2 H), 1.34–1.23 (m, 1 H), 1.22–1.10 (m, 1 H), 0.84 (s, 9 H), 0.00 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 74.9, 70.5, 64.8, 52.5, 51.8, 36.8, 28.5, 25.8, 25.0, 23.8, 18.0, –4.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{31}NO_3SiNa$: 336.1967; found: 336.1971.

(1*R*,3*S*,8a*S*,*Z*)-1-(*tert*-Butyldimethylsiloxy)-3-[4-(triisopropylsilyl)but-1-en-3-ynyl]octahydroindolizine (14)

Step 1: DIBAL-H Reduction: To a solution of **7** (204 mg, 0.65 mmol) in anhyd toluene (10 mL) at –78 °C was added 1.1 M DIBAL-H in THF (1.2 mL, 1.3 mmol, 2 equiv) over a period of 5 min. After 2 h at –78 °C, anhyd EtOH (4 mL) was added and the reaction mixture was allowed to warm to –20 °C. A 1 M solution of potassium sodium tartrate in H_2O (6.5 mL, 10 equiv) was added and the biphasic solution was vigorously stirred for 1 h while warming to r.t. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the corresponding aldehyde as a pale, yellow oil; it was used without further purification in the olefination step.

Step 2: Peterson Olefination: An oven-dried Schlenk tube equipped with a magnetic stirring bar and an argon inlet was charged with 1,3-bis(triisopropylsilyl)prop-1-yne **13** (337 mg, 0.957 mmol, 1.5 equiv) in anhyd THF (3.5 mL) and cooled to –20 °C. A 1.6 M solution of *n*BuLi in hexanes (0.6 mL, 0.957 mmol, 1.5 equiv) was added dropwise and the resulting yellow solution was stirred for 20 min at –20 °C and then cooled to –78 °C. A solution of the above prepared aldehyde in THF (5 mL) was added dropwise. The resulting mixture was stirred for 2 h at –78 °C and was then warmed to r.t. over 6 h. The reaction was quenched by the addition of H_2O (20 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, cyclohexane/EtOAc 10:0 to 8:2) to afford the corresponding *Z*-diene.

Yield: 156 mg (0.0.338 mmol, 52% over the two steps); oil; $[\alpha]_D^{20}$ –46 (*c* 1.5, $CHCl_3$).

IR (film): 2936, 2864, 1463, 1257, 1143, 1071, 836, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.82 (t, *J* = 10.6 Hz, 1 H), 5.61 (d, *J* = 10.6 Hz, 1 H), 3.91–3.83 (m, 1 H), 3.64–3.57 (m, 1 H), 3.03–2.97 (m, 1 H), 1.97–1.87 (m, 3 H), 1.84–1.79 (m, 2 H), 1.62–1.56 (m, 2 H), 1.45–1.39 (m, 1 H), 1.23–1.17 (m, 2 H), 1.08 (s, 21 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 111.6, 103.2, 96.1, 75.8, 71.0, 62.9, 51.7, 39.3, 29.0, 25.8, 25.3, 23.9, 18.7, 18.1, 11.3, –4.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{52}NOSi_2$: 462.3587; found: 462.3591.

(1*R*,3*S*,8a*S*,*Z*)-3-(But-1-en-3-ynyl)octahydroindolizin-1-ol (15)

To a solution of **14** (150 mg, 0.324 mmol) in anhyd THF (5 mL) at 0 °C under argon was added via syringe a solution of TBAF (178 mg, 0.682 mmol, 2.1 equiv) in anhyd THF (3 mL). The resulting solution was stirred at 0 °C for 3.5 h. Then the solvent was removed in vacuo and the crude material was subjected to flash chromatography (silica gel, cyclohexane/EtOAC 8:2 to 2:8).

Yield: 37 mg (0.194 mmol, 60%); white solid; $[\alpha]_D^{20}$ –63 (*c* 1.1, $CHCl_3$).

IR (film): 3295, 2934, 2853, 1652, 1441, 1258, 1139 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.86 (dd, *J* = 10.6 Hz, 8.9 Hz, 1 H), 5.57 (d, *J* = 10.6 Hz, 1 H), 3.97–3.92 (m, 1 H), 3.56 (q, *J* = 8.5 Hz, 1 H), 3.08 (dd, *J* = 0.9 Hz, 2.4 Hz, 1 H), 3.00–2.98 (m, 1 H), 2.78 (br s, 1 H), 2.00–1.75 (m, 7 H), 1.63 (d, *J* = 12.7 Hz, 1 H), 1.29–1.18 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 110.9, 82.3, 79.9, 74.9, 71.8, 62.8, 51.5, 39.0, 28.8, 25.0 23.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}NO$: 192.1388; found: 192.1381.

(3*S*,8a*S*,*Z*)-3-(But-1-en-3-ynyl)hexahydroindolizin-1(5*H*)-one (6)

An oven-dried Schlenk tube equipped with a stirring bar and an argon inlet was charged with a solution of oxalyl chloride (48 µL, 0.564 mmol, 1.2 equiv) in CH_2Cl_2 (2 mL) and cooled at –78 °C. A solution of DMSO (83 µL, 1.175 mmol, 2.5 equiv) in CH_2Cl_2 (2 mL) was added and the resulting mixture was stirred for 10 min. Then, a solution of alcohol **15** (90 mg, 0.47 mmol) in CH_2Cl_2 (2 mL) was slowly added and the solution was stirred for 1 h at –78 °C prior to the addition of Et_3N (320 µL, 2.35 mmol, 5 equiv). After 15 min, the reaction mixture was allowed to warm to r.t. over a period of 30 min. Upon completion (TLC monitoring), the reaction was quenched by addition of brine (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (silica gel, cyclohexane/EtOAc 8:2 to 7:3 + 1% Et_3N) afforded **6**.

Yield: 80 mg (0.423 mmol, 90%); amorphous white solid; $[\alpha]_D^{20}$ –65 (*c* 5, $CHCl_3$).

IR (film): 3288, 2937, 2857, 1733, 1583, 1439, 1099, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.93 (t, *J* = 9.9 Hz, 1 H), 5.70 (dd, *J* = 9.9 Hz, 1.7 Hz, 1 H), 3.72 (q, *J* = 8.7 Hz, 1 H), 3.18–3.14 (m, 1 H), 3.14 (s, 1 H), 2.55 (dd, *J* = 18.3 Hz, 6.4 Hz, 1 H), 2.29–2.24 (m, 1 H), 2.14–2.05 (m, 2 H), 2.03–1.97 (m, 1 H), 1.89–1.83 (m, 1 H), 1.71–1.58 (m, 2 H), 1.52–1.45 (m, 1 H), 1.30–1.23 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.4, 144.2, 112.2, 83.0, 79.5, 70.0, 60.4, 51.6, 42.0, 25.5, 25.2, 23.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO$: 190.1232; found: 190.1311.

Allosecurinine (3)

An oven-dried vial equipped with a stirring bar was charged with $W(CO)_6$ (303 mg, 0.862 mmol, 2.5 equiv) and sealed with a crimp cap. The vial was evacuated and flushed with CO (3×). Then, a solution of **6** (65 mg, 0.354 mmol) in toluene/DMF (1.5 mL/0.9 mL) was added via syringe. The resulting mixture was stirred for 0.5 h at 140 °C and then cooled to r.t. The content of the vial was transferred into a round-bottom flask and concentrated in vacuo. The resulting black residue was subjected to flash chromatography (silica gel, toluene/EtOAc, 95:5 to 85:15 +1% Et_3N) to afford allosecurinine/phyllochrysine (**3**).

Yield: 9 mg (0.041 mmol, 12%); yellow solid; $[\alpha]_D^{20}$ –1033 (*c* 2, EtOH).

The analytical data were identical to those reported in the literature.[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (dd, *J* = 5.2 Hz, 8.8 Hz, 1 H), 6.64 (d, *J* = 9.2 Hz, 1 H), 5.72 (s, 1 H), 3.90 (t, *J* = 4.6 Hz, 1 H), 3.65 (dd, *J* = 3.2 Hz, 13.4 Hz, 1 H), 2.76–2.73 (m, 2 H), 2.68 (dd, *J* = 4.2 Hz, 9.6 Hz, 1 H), 1.91 (d, *J* = 9.8 Hz, 1 H), 1.72–1.64 (m, 3 H), 1.47–1.32 (m, 2 H), 1.19–1.08 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 167.4, 148.5, 122.7, 109.0, 91.6, 60.7, 58.8, 43.6, 42.6, 22.1, 21.0, 18.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{15}NO_2Na$: 240.1000; found: 240.1001.

Acknowledgment

Université Paris Descartes and CNRS are gratefully acknowledged for their financial support. P. Leproux (UMR CNRS 8638, Université Paris Descartes) is acknowledged for her technical assistance (mass spectrometry). F.H.P. thanks E. P. Santos (Antoine Béclère Hospital) for her technical assistance during the preparation of the manuscript.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612063.

References

(1) Present address: CEA IBiTec-S/SCBM, CEA Saclay, Labex LERMIT, 91191 Gif-sur-Yvette, France.
(2) (a) Wehlauch, R.; Gademann, K. *Asian J. Org. Chem.* **2017**, *6*, 1146. (b) Chirkin, E.; Atkatlian, W.; Porée, F.-H. *The Securinega Alkaloids*, In *The Alkaloids, Vol. 74*; Knölker, H.-J., Ed.; Academic Press: New York, **2015**, 1–120. (c) Snieckus, V. *The Securinega Alkaloids*, In *The Alkaloids, Vol. 14*; Manske, R. H. F., Ed.; Academic Press: New York, **1973**, 425–506.
(3) Zhang, H.; Zhu, K.-K.; Gao, X.-H.; Yue, J.-M. *Tetrahedron* **2017**, *73*, 4692.
(4) Weinreb, S. M. *Nat. Prod. Rep.* **2009**, *26*, 758; see also ref. 1.
(5) (a) Wei, H.; Qiao, C.; Liu, G.; Yang, Z.; Li, C. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 620. (b) Wehlauch, R.; Grendelmeier, S. M.; Miyatake-Ondozabal, H.; Sandtorv, A. H.; Scherer, M.; Gademann, K. *Org. Lett.* **2017**, *19*, 548.
(6) Beutler, J. A.; Karbon, E. W.; Brubaker, A. N.; Malik, R.; Curtis, D. R.; Enna, S. *J. Brain Res.* **1985**, *330*, 135.
(7) (a) Rana, S.; Gupta, K.; Gomez, J.; Matsuyama, S.; Chakrabarti, A.; Agarwal, M. L.; Agarwal, A.; Agarwal, M. K.; Wald, D. N. *FASEB J.* **2010**, *24*, 2126. (b) Gupta, K.; Chakrabarti, A.; Rana, S.; Ramdeo, R.; Roth, B. L.; Agarwal, M. L.; Tse, W.; Agarwal, M. K.; Wald, D. N. *PloS One* **2011**, *6*, e21203. (c) Li, M.; Han, S.; Zhang, G.; Wang, Y.; Ji, Z. *Pharmazie* **2014**, *69*, 217. (d) Chen, C. R.; Xia, X. H.; Yao, S. Y.; Zhang, Q.; Wang, Y.; Ji, Z. *Pharmazie* **2012**, *67*, 351.
(8) (a) Perez, M.; Ayad, T.; Maillos, P.; Poughon, V.; Fahy, J.; Ratovelomanana-Vidal, V. *Eur. J. Med. Chem.* **2016**, *109*, 287. (b) Klochkov, S. G.; Afanas'eva, S. V.; Grigor'ev, V. V. *Chem. Nat. Compd.* **2008**, *44*, 197.
(9) Gundluru, M. K.; Agarwal, M.; Xia, Z.; Karan, G.; Wald, D. N. Patent WO2015051276 A1, **2015**.
(10) (a) Zhang, H.; Zhu, K. K.; Han, Y. S.; Luo, C.; Wainberg, M. A.; Yue, J. M. *Org. Lett.* **2015**, *17*, 6274. (b) Zhang, H.; Zhang, C. R.; Han, Y. S.; Wainberg, M. A.; Yue, J. M. *RSC Adv.* **2015**, *5*, 107045.
(11) For selected recent syntheses of securinega alkaloids, see: (a) Jeon, S.; Han, S. *J. Am. Chem. Soc.* **2017**, *139*, 6302. (b) Han, H.; Smith, A. B. III. *Org. Lett.* **2015**, *17*, 4232. (c) Ma, N.; Yao, Y.; Zhao, B. X.; Wang, Y.; Ye, W. C.; Jiang, S. *Chem. Commun.* **2014**, *50*, 9284. (d) ElSohly, A. M.; Wespe, D. A.; Poore, T. J.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 5789. (e) Chen, J. H.; Levine, S. R.; Buergler, J. F.; McMahon, T. C.; Medeiros, M. R.; Wood, J. L. *Org. Lett.* **2012**, *14*, 4531. (f) Leduc, A. B.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 7945.
(12) Chirkin, E.; Michel, S.; Porée, F.-H. *J. Org. Chem.* **2015**, *80*, 6525.
(13) Friedman, R. K. *Ph.D. Thesis*; Colorado State University: USA, **2010**.
(14) For recent use of oxa-HPK in total synthesis, see: (a) Tao, C.; Zhang, J.; Chen, X.; Wang, H.; Li, Y.; Cheng, B.; Zhai, H. *Org. Lett.* **2017**, *19*, 1056. (b) Lu, H. H.; Martinez, M. D.; Shenvi, R. A. *Nat. Chem.* **2015**, *7*, 604. (c) Chen, J.; Gao, P.; Yu, F.; Yang, Y.; Zhu, S.; Zhai, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 5897.
(15) (a) Zhang, X.; Schmitt, A. C.; Jiang, W. *Tetrahedron Lett.* **2001**, *42*, 5335. (b) Dhudshia, B.; Cooper, B. F. T.; Macdonald, C. L. B.; Thadani, A. N. *Chem. Commun.* **2009**, 463.
(16) The spectroscopic data of 11 correspond to those in ref. 15. For the initial report on the preparation of 11 in a stereoselective manner and via a different strategy (both enantiomers), see: Katoh, M.; Matsune, R.; Honda, T. *Heterocycles* **2006**, *67*, 189.
(17) Katoh, M.; Mizutani, H.; Honda, T. *Heterocycles* **2006**, *69*, 193.
(18) (a) Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc.* **2004**, *126*, 12432. (b) Corey, E. J.; Rucker, C. *Tetrahedron Lett.* **1982**, *23*, 719.
(19) The data for the synthetic sample were identical to those reported in the literature; see: Levant, P. D.; Beutler, J. A. *Tetrahedron* **1987**, *43*, 2915.