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Brief Communication

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Viability of a [2 + 2 + 1] Hetero-Pauson–Khand Cycloaddition Strategy toward *Securinega* Alkaloids: Synthesis of the BCD-Ring Core of Securinine and Related Alkaloids

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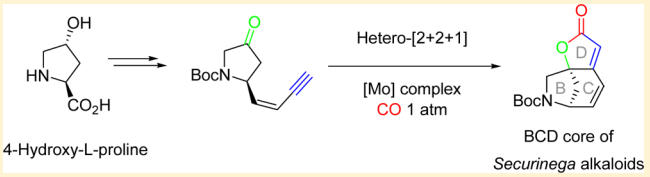
Supporting Information

ABSTRACT: Preliminary results related to the development of [2 + 2 + 1]-oxa-hetero-Pauson–Khand cycloaddition strategy toward the *Securinega* alkaloids are reported. The critical tricyclic BCD-ring core was assembled in only nine linear steps from cheap 4-hydroxy-L-proline. The study provides valuable insight into the scope of a rare hetero-Pauson–Khand reaction, a powerful tool for the rapid construction of butenolide-containing natural products.



Securinega alkaloids are a group of about 60 secondary metabolites, isolated from plants belonging to the *Securinega* (*Flueggea*), *Phyllanthus*, *Breynia*, and *Margaritaria* genera, Phyllanthaceae family.[1] Characteristic to these compounds is a unique tetracyclic ABCD structure featuring a strained α,β-unsaturated γ-lactone moiety as exemplified with securinine (**1**), phyllanthidine (**2**), and norsecurinine (**3**) (Figure 1).

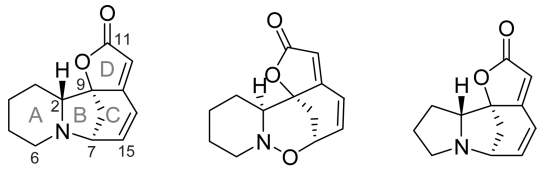


Figure 1. Structures of some representative *Securinega* alkaloids.

Securinine (**1**), the most abundant alkaloid in this family, was previously marketed for its CNS properties.[2] Besides antiplasmodial, antibacterial, and antifungal activities reported for *Securinega* alkaloids,[3] securinine (**1**) induces apoptosis of several cancer cell lines.[4]

Because of their intriguing structure and promising biological activities, the *Securinega* alkaloids have been the subject of a comprehensive synthetic work.[5] The most daunting challenge to synthetic chemists is the construction of the critical butenolide-containing CD motif. Considering the CD ring system in the *Securinega* alkaloids as the result of a formal [2 + 2 + 1] cycloaddition, one could expect to forge it in a single synthetic operation. To the best of our knowledge, the only attempt to apply an oxa-hetero-Pauson–Khand cycloaddition (HPK) to total synthesis in this alkaloid series met with failure.[6] Recently, the *Securinega* CD-motif **4** was accessed via a complementary NHC-catalyzed [3 + 2]-addition of an ynal onto a ketone, albeit in a moderate 31% yield (Scheme 1).[7]

Despite its attractiveness, the disclosed approach required rather fine-tuned reaction conditions limiting its versatility. A flexible synthetic access to securinine (**1**) and its congeners would lead to identification of the pharmacophore and therefore could give rise to novel promising analogues. On the other hand, the scope and boundaries of HPK remain widely unknown. Few examples of HPK applied to total synthesis of natural products can be cited, and the literature precedents are mainly confined to the use of aldehydes as ene partner.[8,9] Preliminary studies into the viability of a Mo-mediated intramolecular oxa-HPK of a ketone and terminal alkyne applied to the synthesis of the *Securinega* alkaloid BCD-ring core **4** are described herein.

Our synthetic plan to access **4** involved preparation of (*Z*)-enyne **5** from 4-hydroxy-L-proline (**7**) (Scheme 2). Of note, the stereochemistry of the target butenolide **4** would be secured by the built-in chirality of **7**. Aldehyde **6**[7] obtained in 76% yield from (**7**) was subjected to a Julia–Kocienski olefination with readily available propargyl sulfone **8**[10,11] to efficiently install the requisite *Z*-enyne fragment (*Z*/*E* 20:1). Upon removal of the silyl protecting groups, Dess–Martin oxidation of **10** to ketone **5** set the stage for the investigation into the strategic cycloaddition event.

Since the seminal work done by Buchwald and Crowe,[12] a plethora of metals has been found to catalyze or to promote HPK.[13] Our choice for $Mo(CO)_3(DMF)_3$ was 2-fold: (1) it is known to be a powerful promoter for HPK[14] and (2) it could be easily prepared[15] from commercial air-stable $Mo(CO)_6$ complex. The first attempt to achieve the key [2 + 2 + 1]-cycloaddition was made by treatment of substrate **5** with 2.5

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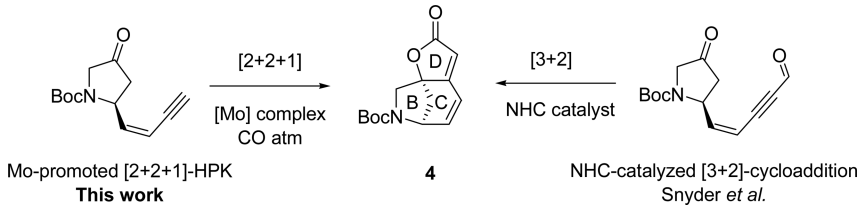
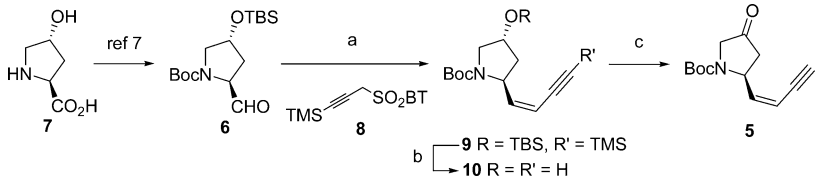
Scheme 1. Strategies for the Construction of the CD-Ring System

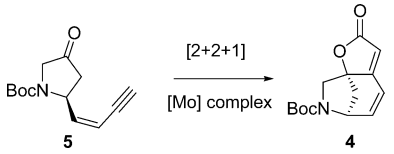


Scheme 2. Preparation of Substrate 5[a]



[a]Reagents and conditions: (a) **8**, NaHMDS, THF, −55 °C (61%, *Z*/*E* 20:1); (b) TBAF, THF, rt (96%); (c) DMP, DCM, rt (87%).

Table 1. Screening of HPK Reaction Conditions



entry[a]	promoter	CO (atm)	solvent	*T* (°C)	time (h)	yield (%)
1	$Mo(CO)_3(DMF)_3$[b]	none	THF	rt	96	5[c]
2	$Mo(CO)_3(DMF)_3$[b]	1	THF	rt	24	traces
3	$Mo(CO)_3(DMF)_3$[b]	none	THF	70	40	5[c]
4	$Mo(CO)_3(DMF)_3$[b]	none	PhMe	rt	24	traces
5	$Mo(CO)_3(DMF)_3$[b]	none	PhMe	140	16	21[c]
6	$Mo(CO)_6$[b]	none	PhMe/DMF	140	2	23[c]
7	$Mo(CO)_6$[b]	1	PhMe/DMF	140	2	50[c]
8	$Mo(CO)_6$[b]	1	PhMe/DMF	100	22	15[c]
9	$Mo(CO)_6$[d]	1	PhMe/DMF	140	2	8[c]
10	$Mo(CO)_6$[e]	1	PhMe/DMF	140	2.5	35[c]
11	$Mo(CO)_6$[f]	1	PhMe/DMF	140	3	19[c]
12	$Mo(CO)_6$[b,g]	1	PhMe/DMF	140	3	traces

[a]All reactions were carried out on 0.33 M scale. [b]Reaction was carried out in the presence of 2.5 equiv of [Mo] complex. [c]Isolated yield. [d]Reaction was carried out in the presence of 5 equiv of [Mo] complex. [e]Reaction was carried out in the presence of 50 mol % of [Mo] complex. [f]Reaction was carried out in the presence of 25 mol % of [Mo] complex. [g]Cyclohexylamine (5 equiv) was added to the reaction mixture.

equiv of $Mo(CO)_3(DMF)_3$ in THF under argon (entry 1, Table 1).[16] Gratifyingly, ca. 5% of the desired butenolide **4** was obtained after 4 days together with an important amount of the unconsumed starting material. With this promising result in hand, we embarked on the optimization of reaction conditions in a stepwise approach. Thus, the same reaction was carried out under 1 atm of CO (entry 2). Curiously, only traces of **4** could be detected. Refluxing in THF did not improve the yield (entry 3) but considerably enhanced the rate of the reaction. In order to fully prevent exposure of the highly instable $Mo(CO)_3(DMF)_3$ to air, its preparation procedure was modified. After $Mo(CO)_6$ was refluxed in a mixture of toluene/DMF and cooled to rt, the solution of **5** in anhydrous toluene was directly added to this suspension via syringe. Very low conversion of the starting material was detected if this procedure was carried at rt, whereas heating at 140 °C overnight dramatically increased the yield to 20−25% (entries 4 and 5). Drawing upon the idea that $Mo(CO)_3(DMF)_3$ underwent a rapid degradation, we switched to a simplified "all-together" procedure, in the course of which $Mo(CO)_3(DMF)_3$ was formed in situ from $Mo(CO)_6$ upon refluxing in toluene/DMF in the presence of **5**. Indeed, this operationally simple procedure was unexpectedly efficient, and the starting material was completely consumed within 2 h (entry 6). The same reaction carried under CO atmosphere (1 atm) further increased the yield to 50% (entry 7). Additional attempts to optimize the yield by modifying the reaction temperature or the promoter loading or by addition of an amine[17] were unfruitful (entries **8**−**12**).

In summary, the first successful application of HPK to the critical BCD-core of *Securinega* alkaloids is reported. Despite its rather moderate yield, the disclosed approach proves the viability of the HPK cycloaddition strategy toward the intricate architecture of *Securinega* alkaloids. We anticipate the developed synthetic route will be valuable for the preparation of various natural *Securinega* alkaloids as well as their unnatural analogues which are otherwise inaccessible by semisynthetic modifications. Currently, we are pursuing the application of this

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methodology to the total synthesis of securinine (**1**) and norsecurinine (**2**).

EXPERIMENTAL SECTION

(2*S*, 4*R*)-*tert*-Butyl 2-[(*Z*)-4-(Trimethylsilyl)but-1-en-3-ynyl]-4-(*tert*-butyldimethylsiloxy)pyrrolidine-1-carboxylate (9). An oven-dried Schlenk-tube equipped with a magnetic stirring bar and an argon inlet adapter was charged with aldehyde **6** (0.363 g, 1.10 mmol, 1.6 equiv) and sulfone **8** (0.213 g, 0.688 mmol, 1 equiv) in THF (30 mL). NaHMDS (435 μL, 1.9 M in THF, 0.826 mmol, 1.2 equiv) was added dropwise to this solution at −55 °C. The resulting yellow-orange solution was stirred for 4 h at −55 °C and allowed to warm to rt for 1 h. The mixture was diluted with Et_2O and brine. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (cyclohexane/EtOAc, 9:1) afforded **9** as a yellowish oil (0.177 g, 0.42 mmol, 61%, *Z*/*E* 20:1): $[\alpha]^{20}_D$ +85.0 (*c* 0.08, $CHCl_3$); IR (film) ν 2956, 1696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04−5.77 (m, 1H), 5.48 (d, *J* = 10.5 Hz, 1H), 4.85 (q, *J* = 7.6 Hz, 1H), 4.33 (bs, 1H), 3.55−3.32 (m, 2H), 2.25−2.10 (m, 1H), 1.76−1.67 (m, 1H), 1.45 (s, 9H), 0.89 (s, 9H), 0.19 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 146.7, 108.3, 101.2, 79.4, 69.8, 55.7, 55.1, 41.6, 28.4, 25.7, 17.9, −0.1, −4.8; HRMS (ESI) calcd for $C_{22}H_{42}NO_3Si_2$ $[M + H^+]$ 424.2698, found 424.2697.

(2*S*, 4*R*)-*tert*-Butyl 2-[(*Z*)-But-1-en-3-ynyl]-4-hydroxypyrrolidine-1-carboxylate (10). Compound **9** (0.255 g, 0.602 mmol, 1 equiv) was dissolved in THF (7.5 mL), and TBAF (1.80 mL, 1.0 M in THF, 1.80 mmol, 3 equiv) was added. After being stirred for 16 h, the reaction mixture was quenched by addition of brine (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (cyclohexane/EtOAc, 1:0 to 1:1) afforded **10** as a white solid (0.137 g, 0.579 mmol, 96%): $[\alpha]^{20}_D$ (*c* 0.09, $CHCl_3$) +128.9; IR (film) ν 3402, 2977, 1667, 1403 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01−5.80 (m, 1H), 5.47 (d, *J* = 10.1 Hz, 1H), 4.91 (q, *J* = 8.1 Hz, 1H), 4.44−4.39 (m, 1H), 3.61−3.44 (m, 2H), 3.14 (s, 1H), 2.32−2.22 (m, 1H), 1.90 (br s, 1H, −O*H*), 1.83−1.71 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 146.7, 107.7, 82.9, 79.9, 79.6, 69.6, 55.4, 55.1, 40.8, 28.5; HRMS (ESI) calcd for $C_{13}H_{20}NO_3$ $[M + H^+]$ 238.1438, found 238.1438.

(*S*)-*tert*-Butyl 2-((*Z*)-But-1-en-3ynyl)-4-oxopyrrolidine-1-carboxylate (5). Dess−Martin periodinane (DMP) (0.235 g, 0.55 mmol, 1.25 mmol) was added in one portion to a solution of **10** (0.105 g, 0.44 mmol, 1 equiv) in DCM (5.5 mL) at rt. The reaction mixture was stirred for 2 h, and then a saturated aqueous $NaHCO_3$ solution (6 mL) was added. The mixture was diluted with EtOAc (6 mL), and solid $Na_2S_2O_3$ (ca. 1.0 g) was added. The resulting biphasic mixture was stirred vigorously for 10 min, and the layers were separated. The aqueous phase was extracted with DCM (2 × 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (cyclohexane/EtOAc, 2:1) afforded **5** as a colorless oil (0.090 g, 0.38 mmol, 87%) that turns yellow upon exposure to air: $[\alpha]^{20}_D$ (*c* 0.12, $CHCl_3$) +170.0; IR (film) ν 3290, 2931, 1760, 1392 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (t, *J* = 8.6 Hz, 1H), 5.57 (d, *J* = 10.4 Hz, 1H), 5.22 (t, *J* = 7.5 Hz, 1H), 3.92 (br d, *J* = 19.3 Hz, 1H), 3.75 (br d, *J* = 19.4 Hz, 1H), 3.20 (s, 1H), 2.98 (dd, *J* = 9.8, 18.9 Hz, 1H), 2.38 (d, *J* = 19.0 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 154.0, 144.3, 109.2, 83.9, 80.9, 79.1, 53.8, 52.8, 43.6, 28.4; HRMS (ESI) calcd for $C_{13}H_{17}NO_3Na$ $[M + Na^+]$ 258.1106, found 258.1109.

Butenolide (4). A vial was charged with $Mo(CO)_6$ (0.042 g, 0.159 mmol, 2.5 equiv) and sealed with a crimp cap. The vial was evacuated and flushed with CO (three times). Then a solution of **5** (0.015 g, 0.064 mmol, 1 equiv) in toluene/DMF (1.2 mL/0.7 mL) was added via a syringe. The resulting mixture was stirred for 2 h at 140 °C and then cooled to rt, and the content of the vial was removed to a round-bottom flask. Evaporation of the solvent afforded a black residue which was subjected to flash chromatography (cyclohexane/EtOAc, 2:1) to give **4** as a white solid (8.5 mg, 0.032 mmol, 50%). The analytical data were identical to those reported by Snyder et al.:[7] $[\alpha]^{20}_D$ (*c* 0.13, $CHCl_3$) −363.0; IR (film) ν 2924, 1797, 1693, 1413 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 and 6.80 (rotamers, dd, *J* = 8.2, 5.7 Hz, 1H), 6.57 (d, *J* = 8.5 Hz, 1H), 5.75 (s, 1H), 4.71 and 4.59 (rotamers, t, *J* = 4.5 Hz, 1H), 3.79 (d, *J* = 10.1 Hz, 1H), 3.36 and 3.29 (rotamers, d, *J* = 10.5 Hz, 1H), 2.66 and 2.59 (rotamers, dd, *J* = 10.0, 4.6 Hz, 1H), 1.97 (d, *J* = 9.8 Hz, 1H), 1.46 and 1.43 (rotamers, s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 167.7, 153.9, 143.8, 143.0, 121.9, 121.7, 108.9, 108.6, 87.4, 86.8, 80.7, 80.6, 54.2, 53.3, 50.1, 49.7, 42.7, 42.3, 28.3; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{18}NO_4$ $[M + H^+]$ 264.1230, found 264.1230.

ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra of compounds **4**−**6**, **9**, and **10**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01118.

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Notes

The authors declare no competing financial interest.

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