Total Synthesis of (±)-Setigerumine I: Biosynthetic Origins of the Elusive Racemic *Papaveracaea* Isoxazolidine Alkaloids

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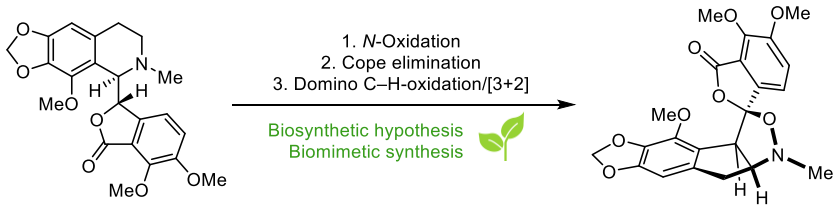
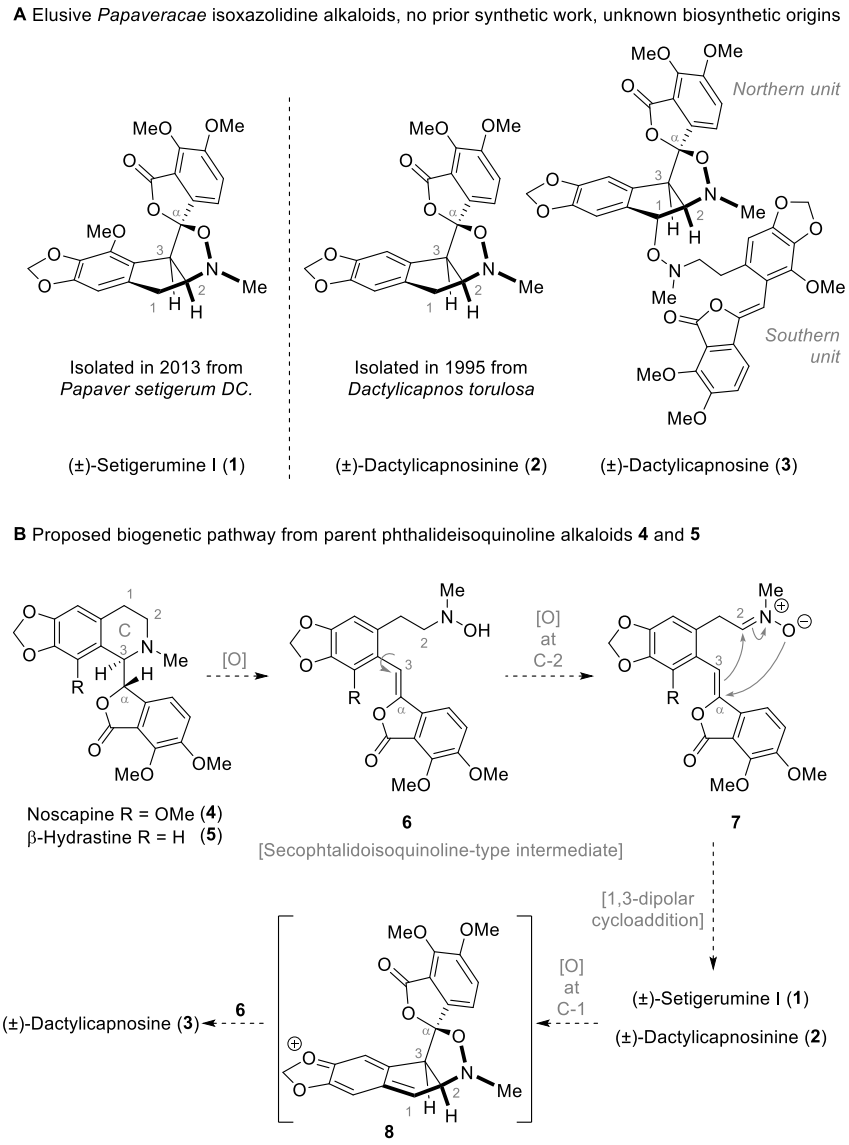


Abstract: The biosynthetic origins of the structurally related racemic isoxazolidine *Papaveracaea* alkaloids Setigerumine I, Dactylicapnosinine and Dactylicapnosine have remained elusive since their original isolation over two decades ago. Herein we report the first biosynthetic hypothesis for their formation and, inspired by it, the first synthesis of (±)-Setigerumine I with accompanying computational rationale. Based on the results, these isoxazolidine alkaloids arise from racemizing oxidative rearrangements of prominent isoquinoline alkaloids Noscapine and Hydrastine. The key steps featured in this synthesis are a room temperature Cope elimination and a domino C–H oxidation/inverse-electron demand 1,3-dipolar cycloaddition of an axially chiral, yet configurationally unstable, intermediate.

Isoquinoline alkaloids, such as morphine, are among the earliest compounds to be used by humans to treat illnesses.[1] Numerous prominent isoquinoline alkaloids have since been isolated and used as pharmaceuticals.[1] Despite almost a 100 years of studies into this vast family of alkaloids, several benzylisoquinoline alkaloids remain elusive. Three such trace alkaloids are naturally racemic Setigerumine I (**1**), Dactylicapnosinine (**2**) and Dactylicapnosine (**3**), that have been isolated from *Papaveracae* family plants in 1995 [for Dactylicapnosinine (**2**) and Dactylicapnosine (**3**)] and 2013 [Setigerumine I (**1**)] (Scheme 1A).[2,3] These alkaloids are structurally unique as they feature a central spiro-isoxazolidine ring and also constitute the only known example of an entire group of structurally related benzylisoquinoline alkaloids, which occur naturally as racemates. Since their isolation, the biosynthetic origins and the chemical synthesis of these obscure racemic alkaloids have remained elusive.

We envisioned that through the total synthesis of Setigerumine I (**1**), we would be able to elucidate a plausible biosynthesis and understand why not only Setigerumine I (**1**), but also Dactylicapnosinine (**2**) and Dactylicapnosine (**3**) exist in Nature as racemates.[4–6] Our synthetic work began by carefully analyzing the unique connectivity in the structures of the target molecules. Setigerumine I (**1**) is structurally related to Dactylicapnosine (**3**), which has a pronounced pseudo-dimeric structure (Scheme 1A). The pseudo-dimeric structure of Dactylicapnosine (**3**) incorporates in its structure a possible clue to the biogenesis of this alkaloid family: the northern and southern pseudo-dimeric units of Dactylicapnosine (**3**) can be mapped onto two known phtalideisoquinoline alkaloids Noscapine (**4**) and Hydrastine (**5**). Both alkaloids are known to occur in *Papaveracae* family plants and could therefore likely be the corresponding biogenetic starting materials.[2,7]



Scheme 1: A: Structurally related racemic isoxazolidine alkaloids Setigerumine I (**1**), Dactylicapnosinine (**2**) and Dactylicapnosine (**3**) all share the same spirocyclic core. **B:** Proposed biosynthetic connection of isoxazolidine alkaloids **1**–**3** to known phtalideisoquinoline alkaloids Noscapine (**4**) and β-Hydrastine (**5**) *via* an oxidative rearrangement pathway.

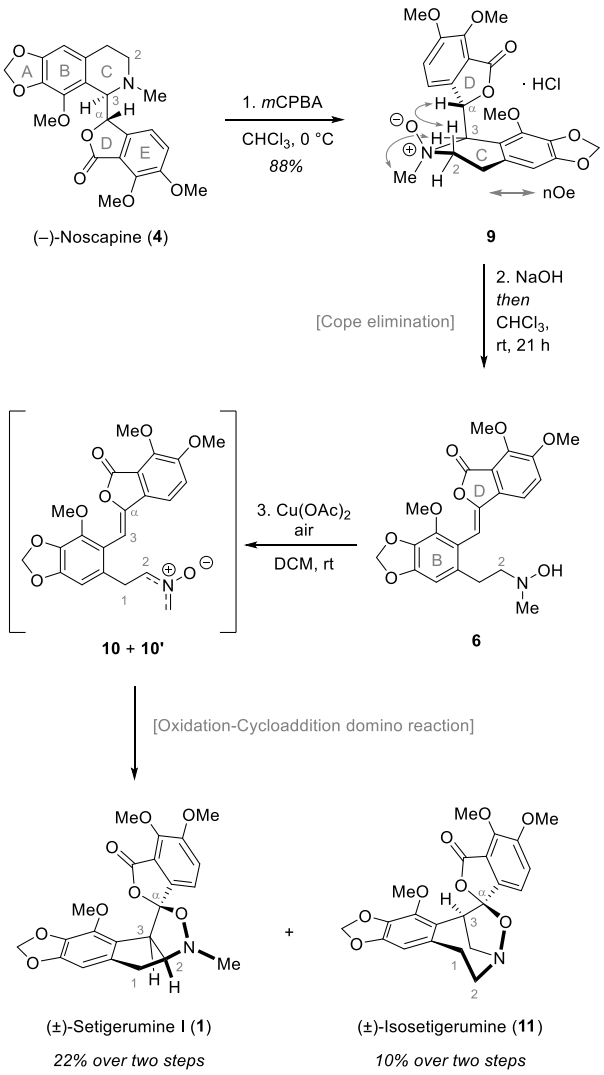
Considering an oxidative rupture of the C-ring of the phtalideisoquinoline core of the proposed biosynthetic starting materials **4** or **5**, an intermediate hydroxylamine secophtalidoisoquinoline **6** could form (Scheme 1B). This Cope elimination reaction could proceed through the formation of Noscapine-*N*-oxide, which is known to form *via* P450 oxidation of Noscapine (**4**).[8–11] If the axial chirality, transferred to **6** from enantiopure parent phtalideisoquinoline alkaloid, is scrambled due to interconversion of rotamers, all materials downstream from this precursor **6** would be racemic. Further C–H oxidation of **6** could generate a nitrone dipole **7**, which could take part in an intramolecular 1,3-dipolar cycloaddition with the previously generated enol-lactone dipolarophile. The 1,3-dipolar cycloaddition would in turn forge the spirocyclic isoxazolidine core of Setigerumine I (**1**), Dactylicapnosinine (**2**) and Dactylicapnosine (**3**). This

proposal agrees with the general tendency of racemic natural products to arise *via* the facile cyclization of achiral precursors.[12,13] Further corroborating this logic, the southern fragment of Dactylicapnosine (**3**) incorporates the putative biosynthetic seco-isoquinoline intermediate **6** in its structure. Therefore, a plausible pathway for the formation of **3** involves a final C–H oxidation at the benzylic site of **2** to form the *para*-quinone-methide **8**. Subsequent nucleophilic attack at C-1 by the hydroxylamine moiety of **6** would furnish the pseudo-dimeric alkaloid **3**. Herein we report the total synthesis of (±)-Setigerumine I (**1**) inspired by this biosynthetic proposal.

We initiated our synthetic campaign toward (±)-Setigerumine I (**1**) by first considering the oxidation of the commercially available parent isoquinoline alkaloid (–)-Noscapine (**4**) to Noscapine-*N*-oxide hydrochloride (**9**). This would set the stage for a Cope-elimination to rupture the isoquinoline C-ring, giving the *seco* enol-lactone **6**. While the *N*-oxidation of Noscapine (**4**) with *m*-CPBA, H_2O_2 and enzymatic methods have been reported in the literature, the configuration of the *N*-oxide product **9** had not been determined.[14–17] Toward this end, Noscapine (**4**) was oxidized with *m*-CPBA in chloroform at 0 °C to Noscapine-*N*-oxide hydrochloride (**9**), which, after an extractive work-up, gave the pure *syn*-stereoisomer in 88% yield.[16] The *syn* configuration of the *N*-oxide **9** was determined by characteristic NOE correlations from phtalide D ring H-α to tetrahydroquinoline C ring H-$2_{pseudoax}$, and from tetrahydroquinoline C ring H-3 to *N*-Me hydrogens H-Me (Scheme 2, inset). To obtain high-purity *syn*-Noscapine-*N*-oxide hydrochloride (**9**), a sequence of consecutive basic, acidic and neutral aqueous washes was developed to remove the unwanted *anti*-diastereomer (See ESI).

Having secured access to Noscapine-*N*-oxide hydrochloride (**9**), we then turned our attention to the Cope-elimination leading to hydroxylamine **6**. As indicated by NOE data, Noscapine-*N*-oxide hydrochloride (**9**) is perfectly predisposed to undergo the desired Cope elimination: the *N*-oxide oxygen is oriented *syn*-periplanar to the phtalide lactone D-ring H-α hydrogen. However, attempts at thermally eliminating the *N*-oxide hydrochloride salt **9** (PhMe, 130 °C) only led to the recovery of the unchanged starting material. We therefore converted the hydrochloride salt **9** to the corresponding free-base by partitioning it between 2.0 M aqueous NaOH and chloroform. In sharp contrast to the reluctance of the hydrochloride salt of **9** to eliminate, the elimination of the free-base **9** proved extremely facile. At room temperature, the spontaneous Cope elimination reached maximum conversion of 71% of **6**, based on ^{1}H NMR, in 21 hours. Compared to the forcing Cope elimination conditions (i.e., usually >100 °C and in non-polar solvents), this transformation (**9** → **6**) proceeds under unusually mild conditions.[18] Product **6** was found to be somewhat unstable and prone to degrade: heating or storing the neat or dissolved material **6** for longer periods of time (>24 h) started consuming **6** to form a previously described 8-membered cyclic hydroxylamine ether.[19] Attempted purification of **6** on silica gel, by either preparative TLC or flash column chromatography, led to full or partial decomposition of the material to a complex mixture. Thankfully, this did not hinder our synthesis, as the crude hydroxylamine product **6** was pure enough to screen the following oxidation step.

We then addressed the oxidation of crude hydroxylamine **6** to the corresponding nitrone **10** for the upcoming dipolar cycloaddition step. Hydroxylamine **6** can undergo a C–H oxidation either at the *N*-Me group or at the C-2 position of the *N*-alkyl group, yielding two possible regioisomeric nitrones **10** and **10'**. We expected the major product to be the desired aliphatic C-2 oxidized nitrone precursor **10** leading to Setigerumine I (**1**), as similar regiochemical oxidation preferences have previously been reported for *N*-methyl-*N*-alkyl hydroxylamines with several different oxidants.[20–23]



Scheme 2: Synthesis of Setigerumine I (**1**) and Isosetigerumine I (**11**). Reagents and conditions: 1. *m*-CPBA (2.0 equiv.), $CHCl_3$, 0 °C, 88%; 2. Basification with 2 M NaOH then $CHCl_3$; rt, 21 h; 3. $Cu(OAc)_2$ (0.1 equiv.), air, DCM, rt, 6 h, regioisomeric ratio 1:2 (based on crude ^{1}H NMR), 32% combined yield over two steps.

Our first choice for the oxidation of hydroxylamine **6** was mercury(II)oxide (HgO), as it has been demonstrated to have a markedly high preference for oxidizing aliphatic groups over *N*-methyl groups for a range of different hydroxylamines.[20,21] To our pleasant surprise, when crude **6** was treated with orange mercury(II)oxide HgO (2.0 equiv., DCM, rt, 3 h), we found that the reaction directly yielded our target molecule (±)-Setigerumine I (**1**) in 27% isolated yield over two steps! This result implies that the *in situ* formed nitrone intermediate **10**, formed upon oxidation of **6**, undergoes a spontaneous 1,3-dipolar cycloaddition to yield Setigerumine I (**1**). It is noteworthy, that similarly to the Cope elimination step, this 1,3-dipolar cycloaddition also takes place under remarkably mild conditions when compared to typically employed approaches (e.g., >100 °C, nonpolar solvents, lengthy reaction times).[24–26] This remarkably concise two-step C–H oxidation/dipolar cycloaddition domino reaction allowed us to complete the first total synthesis of Setigerumine I (**1**) in just three steps from commercially available (–)-Noscapine (**4**).[27–29] In addition to Setigerumine I (**1**), we also isolated the regioisomeric cycloaddition product **11** in 14%

isolated yield. We named this regioisomeric product Isosetigerumine I (**11**). This isomer of Setigerumine I (**1**) results from a similar spontaneous 1,3-dipolar cycloaddition domino reaction of the *N*-methyl oxidized nitrone regioisomer **10'**.

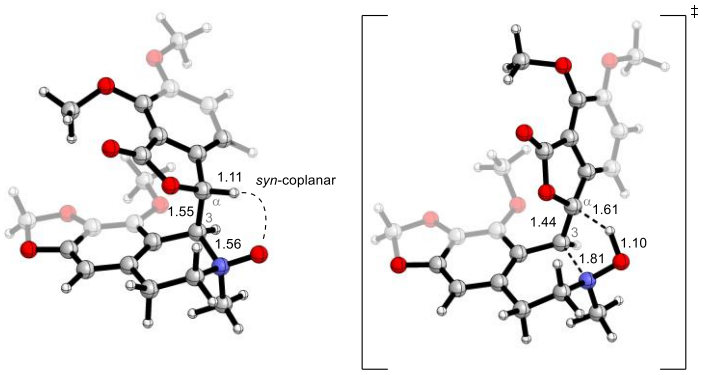
With these encouraging results in hand, showing that upon oxidation hydroxylamine **6** is directly converted to Setigerumine I (**1**) in a C–H oxidation/1,3-dipolar cycloaddition domino reaction, we set out to identify alternative (i.e., less hazardous) oxidants. IBX (1.5 equiv., DCM, rt, 2 h) led to desired hydroxylamine oxidation-cycloaddition domino reaction albeit in lower yields (18% for **1**; 11% for **11**).[30,31] We also considered biomimetic Cu(II) oxidation methods, as numerous aerobic copper-catalyzed oxygenations are established as key steps in important biosynthetic routes, such as the oxidation of polyphenols.[32,33] Under operationally simple aerobic oxidation conditions, that involve bubbling air through a DCM solution of **6** with 10 mol-% of copper(II)acetate as a catalyst, **6** was cleanly converted to Setigerumine I (**1**) in 22% and Isosetigerumine I (**11**) in 10% isolated yields, respectively (Scheme 2).[22] This aerobic copper-catalyzed oxidation method ties back to our biosynthetic hypothesis, and was therefore used as the key preparative method to complete the total synthesis of (±)-Setigerumine I (**1**) on a 20 mg scale and 19% overall yield from (–)-Noscapine (**4**) (Scheme 2).

The ^{1}H and ^{13}C data for synthetic Setigerumine I (**1**) were in full agreement with those reported for the isolated material.[2] At the outset of this study, it was not clear if the axially chiral atropisomer of the hydroxylamine intermediate **6**, formed by Cope elimination of (–)-**4**, would be configurationally stable at room temperature. If the rotational barrier for the interconversion between rotamers of **6** was sufficiently low, the stereochemical information of the parent isoquinoline alkaloid would be lost. As neither synthetic Setigerumine I (**1**) nor Isosetigerumine I (**11**) displayed optical activity, the chiral information of **6** must have been lost. The observed stereochemical scrambling from enantiopure (–)-**4** to racemic (±)-**1** during the course of our biomimetic total synthesis therefore provides an explanation as to why the alkaloid family members **1**, **2** and **3** exist as racemates in Nature.

As Cope eliminations and 1,3-dipolar cycloadditions traditionally occur only at elevated temperatures and in non-polar solvents (i.e., >100 °C, PhMe or benzene), we were intrigued to find that the key steps, Cope elimination **9** → **6** and 1,3-dipolar cycloaddition **10/10'** → **1/11**, of our synthetic route were so facile that both reactions occurred at room temperature.[18] To gain further insights into these facile processes, we embarked on studying these systems computationally. Full conformational space of all stationary points **9**, **6**, **10**, **10'**, **1** and **11** were first studied using metadynamics (GFN2) with crest 2.11/xtb 6.4.0 and the resulting non-degenerate conformers (<10 kcal/mol, 298 K) were further DFT (B97-D3/DEF2SVP) optimized using orca 4.1.2.[34–37] Final DFT geometry optimization and energy calculations were carried out using B97-D3/TZVP level of theory both in gas phase and using CPCM solvent model for chloroform and dichloromethane at 298.15 K. Relevant transition states were identified using climbing image nudged elastic bond method (CI-NEB, B97-D3/DEF2SVP) connecting the stationary points as implemented in orca 4.1.2, and further optimized with higher level DFT (B97-D3/TZVP) in both gas phase and using CPCM solvent model.

Compared to typical Cope-eliminations, where amine *N*-oxides are eliminated at elevated temperatures (e.g., >100 °C), the spontaneous rupture of the C ring of Noscapine-*N*-oxide (**9**) free-base at room temperature constitutes a rare example of an extremely low-temperature Cope elimination.[38–40] Whereas most Cope eliminations require the system to first rotate to a reasonably high-energy *syn*-periplanar conformer, in the case of Noscapine-*N*-oxide (**9**) freebase, the folded scaffold's minimum energy

conformers all display a *syn*-coplanar arrangement of H-α with the *N*-oxide oxygen (Figure 1). This conformational preference is also corroborated by the NOE data we obtained for **9** (Scheme 2). This is reflected in the relevant dihedral angle, as it shows only a slight decrease from $\varphi_{\alpha-3-N-O}$ = 14.7° in the starting material to $\varphi_{\alpha-3-N-O}$ = 3.5° in the transition state. Consequently, the computed solution phase activation energy barrier lies reasonably low at $\Delta G_{TS,\ Cope}$ = 16.1 kcal/mol and $\Delta H_{TS,Cope}$ = 16.5 kcal/mol, as the Noscapine-*N*-oxide (**9**) system does not have to overcome any significant rotational barriers to reach the *syn*-coplanar transition state.



$\varphi_{\alpha-3-N-O}$ = 14.7°

SM$_{\text{Noscapine-}N\text{-oxide}}$

(0.0; 0.0)

$\varphi_{\alpha-3-N-O}$ = 3.5°

TS$_{\text{Cope}}$

(16.1; 16.5)

Figure 1: The facility of the Cope elimination is explained by the close conformational similarity between the minimum energy conformer of the Noscapine-*N*-oxide (**9**) and the resulting transition state. Both display the *N*-oxide *syn*-co-planar with the eliminating hydrogen. Distances are reported in Ångström and solvent energies (ΔG; ΔH) in kcal/mol at 298.15 K relative to the starting material.

The 1,3-dipolar cycloaddition forming Setigerumine I (**1**) and Isosetigerumine I (**11**) also occurs at room temperature, with enol-lactone **6** starting material being consumed in just several hours with all screened oxidants. The uncatalyzed intramolecular dipolar cycloadditions to form Setigerumine I (**1**) and Isosetigerumine I (**11**) proceeded with reasonably low energy barriers in solution $\Delta G_{TS,\ Dipolar}$ = 19.3 kcal/mol; $\Delta H_{TS,Dipolar}$ = 18.6 kcal/mol, and $\Delta G_{TS,\ Dipolar}$ = 17.2 kcal/mol; $\Delta H_{TS,Cope}$ = 16.6 kcal/mol respectively (Figure 2). While these energies agree with our experimental observations, the possible activation of nitrones **10** and **10'** by Lewis-acidic oxidants cannot be ruled out at this stage.[41]

We expected the intramolecular [3+2] reaction, taking nitrone **10** to Setigerumine I (**1**), to be an inverse electron-demand 1,3-dipolar cycloaddition reaction, as the nitrone dipole of **10** reacts with a reasonably electron-rich enol ether dipolarophile. These inverse electron-demand processes are markedly underdeveloped when compared to their normal electron-demand counterpairs.[42–44] As expected, the electron-rich enol ether dipolarophile has a dominant Nu_{alkene}–$E_{nitrone}$ interaction, which is evident from the energetics of the relevant orbitals involved in the reaction.[45] For nitrone **10** forming Setigerumine I (**1**), the $HOMO_{enol}$–$LUMO{+}1_{nitrone}$ = +3.04 eV interaction energy is much lower than the alternative pairing arrangement $HOMO\text{-}19_{nitrone}$–$LUMO_{enol}$ = +6.65 eV (See ESI). In contrast, rather surprisingly, the reaction of nitrone **10'** to form Isosetigerumine I (**11**) is better described as an ambiphilic dipolar cycloaddition, where both the Nu_{alkene}–$E_{nitrone}$ and $Nu_{nitrone}$–E_{alkene} energy gaps are very similar. For nitrone **10'** forming Isosetigerumine I (**11**), the $HOMO_{enol}$–$LUMO{+}1_{nitrone}$ = +2.99 eV interaction energy is very close to the alternative orbital energy gap $HOMO\text{-}2_{nitrone}$–$LUMO_{enol}$ = +3.03 eV (See ESI). Although, intuitively, a

dominant Nu contribution of the electron-rich enol-lactone could be expected for both systems **10** and **10'**, this highlights that the electronic nature of even seemingly similar 1,3-dipolar cycloadditions can be vastly different.

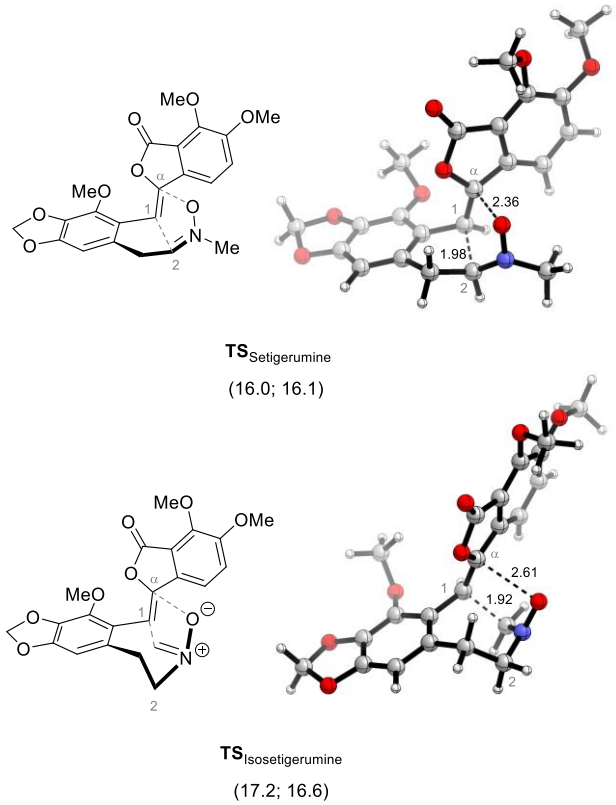


Figure 2: Dipolar cycloaddition transition states leading to Setigerumine I (**1**) and Isosetigerumine (**11**). Distances are reported in Ångström and solvent energies (ΔG; ΔH) in kcal/mol at 298.15 K relative to the starting material.

In conclusion, we have reported the first synthesis of (±)-Setigerumine I (**1**) and chemically demonstrated a plausible oxidative biogenetic pathway for its formation from (–)-Noscapine (**4**) under mild conditions. The proposed biogenetic pathway involves the following steps: (1) *N*-Oxidation of a parent phtalidoisoquinoline alkaloid; (2) Spontaneous room-temperature Cope elimination of the *N*-oxide to form an intermediate secophtalidoisoquinoline; (3) Further oxidation of the secophtalidoisoquinoline to a nitrone, and (4) A spontaneous intramolecular inverse electron-demand 1,3-dipolar cycloaddition of the nitrone to form the rearranged spiro-isoxazolidine alkaloid. Based on these results, the biogenetic origins of all three known spiroketal-isoxazolidine alkaloids Setigerumine I (**1**), Dactylicapnosinine (**2**) and Dactylicapnosine (**3**) can be traced back to similar oxidative rearrangement processes described herein.

Furthermore, the synthesis reported herein showed that both Setigerumine I (**1**) and Isosetigerumine I (**11**) can form as long as the oxidation of the common biosynthetic secophtalidoisoquinoline intermediate **6** is not highly regioselective. Accordingly, if a non-selective oxidation process occurs during their biosynthesis, the side-product of our synthesis, Isosetigerumine I (**11**), may well exist in Nature as a secondary metabolite but has yet to be discovered. Also, as a direct corollary of this work, we postulate that similar rearranged alkaloids derived from other known phtalidoisoquinoline alkaloids: Bicuculline,

Adlumine, and Narcotoline may also exist.[46–49] This is further corroborated by the computational insights, which hint that the required Cope eliminations and 1,3-dipolar cycloadditions can very readily occur under mild conditions in Nature as parts of biosynthetic routes.

Acknowledgements:

We thank Prof. Bang Yeon Hwang at College of Pharmacy, Chungbuk National University for providing the original NMR data for isolated Setigerumine I.

Associated content:

The electronic supporting informational details all experimental and computational work together with NMR data, coordinates and computed energies.

Funding sources:

J. H. S. gratefully acknowledges funding from the Osk. Huttunen Foundation. A. V. S. gratefully acknowledges funding from Zevi & Bertha Salsburg Memorial Fellowship of Rice University. L. K. gratefully acknowledges funding from the National Science Foundation (CHE-2102462), National Institutes of Health (R35 GM-136373), Robert A. Welch Foundation (C-1764).

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