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# Total Synthesis of (+)- and (−)-Decursivine and (±)-Serotobenine through a Cascade Witkop Photocyclization/Elimination/Addition Sequence: Scope and Mechanistic Insights

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**Abstract:** In this article, the total syntheses of antimalarial compound decursivine and its biologically inactive sibling serotobenine are presented. The biomimetic synthesis of (±)-serotobenine was investigated first, but failed. During the subsequent investigation of other synthetic routes, we discovered a new cascade Witkop photocyclization/elimination/addition sequence, which enabled the expedient synthesis of not only racemic decursivine and serotobenine, but also enantiopure (+)- and (−)-decursivine and a variety of their analogues. The present syntheses represent the shortest pathway for the total synthesis of decursivine and serotobenine to date. Moreover, the newly developed cascade sequence for the total synthesis of decursivine does not need any protecting steps. The scope and the reaction mechanism of the cascade sequence were also studied. A rational mechanism for the cascade sequence is proposed, which is consistent with the previous studies and our current experimental results.

**Keywords:** cascade reactions · natural products · photocyclization · reaction mechanisms · total synthesis

## Introduction

Indole alkaloids are the subject of intense investigation in the field of natural product synthesis. Indeed, indoles continue to provide a fertile ground for the discovery and development of new synthesis strategies, new reaction methodologies, and new drug leads.[1]

(+)-Decursivine (**1**) was isolated from the leaves and stems of *Rhaphidophora decursiva* Schott (Araceae) by Fong and co-workers in 2002 during their antimalarial bioassay-directed isolation.[2] It showed antimalarial activity with $IC_{50}$ values of 3.93 and 4.41 $\mu g\,mL^{-1}$ against the D6 and W2 clones of *Plasmodium falciparum*, respectively. During the isolation of (+)-decursivine, a structurally related known indole alkaloid (±)-serotobenine (**2**) was also isolated from the leaf extract. In fact, (±)-serotobenine was first isolated in 1985 and later in 1997 under the name moschamindole.[3,4] Furthermore, serotobenine exists in the racemic form naturally and whose structure is unambiguously assigned by X-ray diffraction. However, unlike decursivine, serotobenine was found inactive against *Plasmodium falciparum*.[2] The only structural difference between decursivine and serotobenine is that the methylenedioxy group in decursivine is opened in serotobenine. This observation indicates that the methylenedioxy group is vital for the biological activity. Very recently, (+)-flavumindole (**3**) and serotobenine were isolated from the leaves and stem bark of *Campylospermum flavum* (Ochnaceae).[5] Flavumindole exhibited no antimicrobial activity. Moschaminindolol (**4**) and moschamine (**5**) were co-isolated with serotobenine (moschamindole), and serotobenine could be formed in vitro from moschamine by either enzymatic (horseradish peroxidase) or non-enzymatic ($K_3Fe(CN)_6$) oxidation.[3] These results implied that decursivine, flavumindole, and serotobenine might share a common biosynthetic pathway.

Decursivine (**1**), serotobenine (**2**), and flavumindole (**3**) have a unique tetracyclic skeleton containing an indole, a dihydrobenzofuran, and an eight-membered lactam bridging the indole 3- and 4-positions (Figure 1). Moschaminindolol (**4**) has an identical structure except for the dihydrofuran ring. The prominent synthetic challenges include the sensitivity of the electron-rich indole to oxidation, the stereogenic centers on the dihydrobenzofuran, and the difficulty in accessing the eight-membered lactam that bridges the indole 3- and 4-positions. The unique structural features and potent biological activity of these alkaloids have inspired numerous synthetic approaches.[6–11] In 2007, Kerr's group reported the first total synthesis of (±)-decursivine in 18 linear steps and 3% overall yield.[6] In 2011, the group of Mascal and our group independently developed a method for the expedient synthesis of (±)-decursivine through a cascade reaction involving Witkop photocyclization.[7,8] In the same year, Li's group accomplished the first asymmetric total synthesis of

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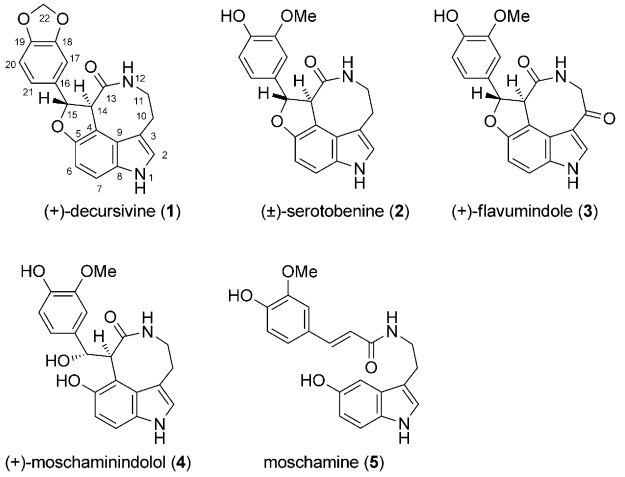
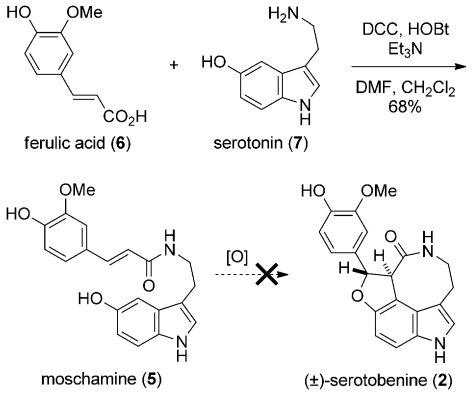



Figure 1. Structures of decursivine and related alkaloids.




Scheme 1. Biomimetic synthesis study.

(+)-decursivine through the phenyliodine bis(trifluoroacetate) (PIFA)-mediated intramolecular [3+2] cycloaddition as the key step.[9] In the meantime, Fukuyama reported the first total synthesis of (−)-serotobenine in 24 linear steps and 8% overall yield.[11] We also applied the Witkop photocyclization methodology to the synthesis of (±)-serotobenine.[8]

Herein, we present a full account of our explorations in the synthesis of this class of natural products, which culminated in the discovery of a new cascade Witkop photocyclization/elimination/addition sequence. The developed cascade sequence enabled the expedient synthesis of not only racemic decursivine and serotobenine, but also enantiopure (+)- and (−)-decursivine, and a variety of analogues of decursivine. In addition, the scope and the reaction mechanism of this cascade sequence were studied.

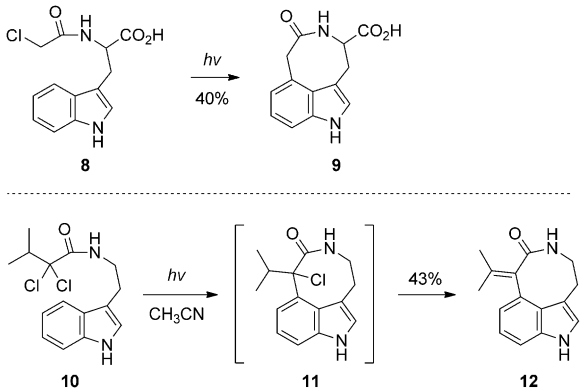
## Results and Discussion

**Biomimetic synthesis of (±)-serotobenine**: Sato and coworkers reported that (±)-serotobenine (**2**) could be produced from moschamine through either enzymatic (horseradish peroxidase) or chemical ($K_3Fe(CN)_6$) oxidation.[3] However, the so-obtained serotobenine was identified by comparing its $R_f$ value on TLC with that of natural serotobenine and no yield was reported. Biomimetic syntheses are often more efficient because of the natural selection. Thus, this biomimetic transformation was investigated first (Scheme 1).

Moschamine (**5**) was synthesized by coupling ferulic acid (**6**) with serotonin (**7**), and the oxidation of **5** with $K_3Fe(CN)_6$ was subsequently examined. However, contrary to Sato's observation, no evidence of the desired product **2** was found. We then screened a variety of conditions for the oxidation of **5** to **2**. Several silver reagents (AgOAc, $Ag_2O$, $Ag_2CO_3$, and $AgNO_3$), copper reagents (CuOAc and $Cu(OAc)_2$), hypervalent iodine reagents (PhIO, $PhI(OAc)_2$, and Kosers reagent), and other oxidants ($Mn(OAc)_2$, $FeCl_3$, and DDQ) in a variety of solvents and at various pH were tested. Unfortunately, no desired product was obtained. Usually, they gave complex products or the starting moschamine (**5**) was decomposed. In fact, Li also observed the same results.[9] In light of these difficulties, we turned our attention to the design of a retrosynthetic strategy by using a powerful cascade reaction.

**Total synthesis of (±)-decursivine and (±)-serotobenine**: The ideal synthesis is currently pursued actively by organic chemists since it encompasses the ideas of atom, step, and redox-economy.[12] Cascade reactions offer an attractive strategy for the ideal synthesis of complicated natural products.[13] Additionally, the avoidance of protecting groups is the major aspect of streamlining the synthesis.[14]

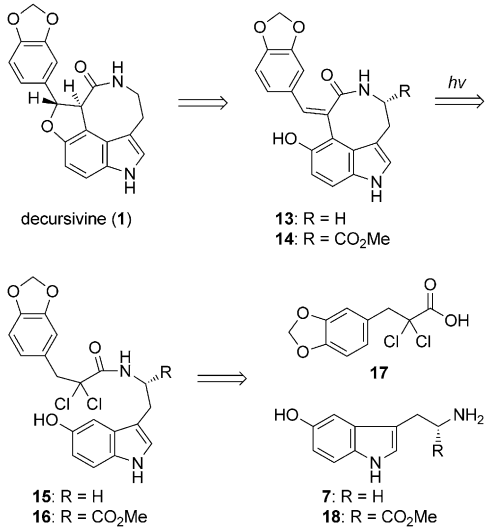
During the course of our synthesis of indole alkaloids,[15] we found that the remarkable Witkop photocyclization could convert the *N*-haloacetyl tryptophan derivative to the eight-membered lactam bridging the indole 3- and 4-positions (Scheme 2).[16–19] However, it has been employed only sporadically in natural product synthesis.[19] Two advantages should be stressed: 1) the direct functionalization of the indole 4-position, but not the more electron-rich indole 2-position, is extremely difficult to carry out in the ground




Scheme 2. Witkop photocyclization.

state; 2) no protecting groups are needed. In 1992, Moody et al. discovered that *N*-dichloroacetyl tryptophan derivatives were better reaction substrates than the monochloro derivatives. In all cases the yields were higher than those obtained from the monochloro derivatives and no evidence of competing cyclization to the indole 2-position was found. Furthermore, they observed that 2,2-dichloro-2-alkyl-amide **10** underwent a cascade photocyclization/elimination sequence to give the α,β-unsaturated lactam **12**.[18a] In fact, Feldman and co-workers have applied this cascade sequence to the synthesis of dragmacidin E.[19b]

We found that lactam **12** contains the three-cyclic system of decursivine. We envisioned that decursivine **1** could be obtained from α,β-unsaturated lactam **13** through either acid-mediated cyclization[20] or an oxidation–cyclization/reduction sequence (Scheme 3).[21] The α,β-unsaturated lactam



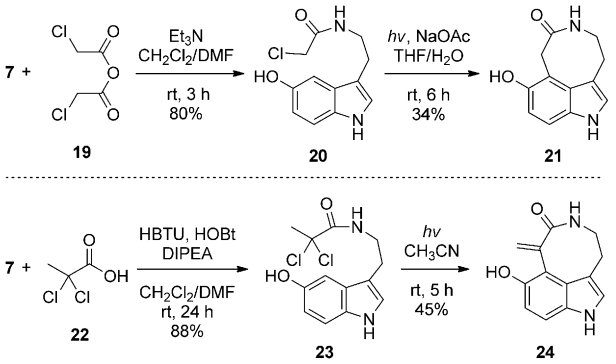

Scheme 3. Retrosynthetic analysis of decursivine.

**13** could be prepared from compound **15** through a Witkop photocyclization/elimination cascade reaction. The precursor **15** in turn could be prepared by coupling acid **17** and serotonin (**7**).

In addition, if this synthetic strategy worked well, starting with enantiopure 5-hydroxy tryptophan **18**, the chirality of the methyl ester of tryptophan could be transferred to the two newly formed chiral centers. Finally, removal of the ester group will provide the optically active decursivine.

To test this concept, we first investigated whether the free phenol can tolerate the reaction conditions. A simple compound **20**, readily prepared through the reaction of serotonin **7** with **19**, was chosen as the model substrate (Scheme 4). We were pleased to find that upon irradiation of chloroacetyl serotonin **20** in THF/$H_2O$ in the presence of NaOAc, the desired product **21** was obtained in 34% yield (not optimized).[16b]

With this promising result, we next turned to investigate the cascade Witkop photocyclization/elimination sequence

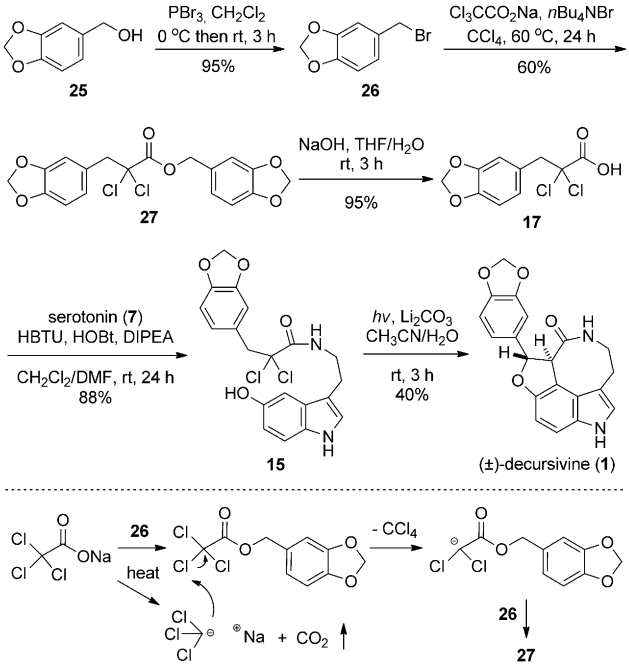



Scheme 4. Model studies.

with compound **23**, which was prepared by condensation of serotonin **7** with 2,2-dichloropropionic acid **22** (Scheme 4). When irradiated in the presence of base, the chloroacetyl serotonin **23** failed to be converted to the desired product **24**. After many trials, we found that irradiation of **23** in $CH_3CN$ in the absence of base could produce the α,β-unsaturated lactam **24** in 45% yield.

With the success of our model studies, we turned our attention to the total synthesis of the decursivine racemate. The synthesis of **1** began with the known compound **26** (Scheme 5), which was readily available from **25** in one step.[22] Double alkylation of sodium trichloroacetate with **26** gave ester **27**, which underwent hydrolysis with NaOH to provide acid **17**.[23] Coupling acid **17** with serotonin **7** by using HBTU afforded the key intermediate **15** in 88% yield.

With compound **15** in hand, the key photocyclization was investigated. Unexpectedly, upon irradiation of **15** in the

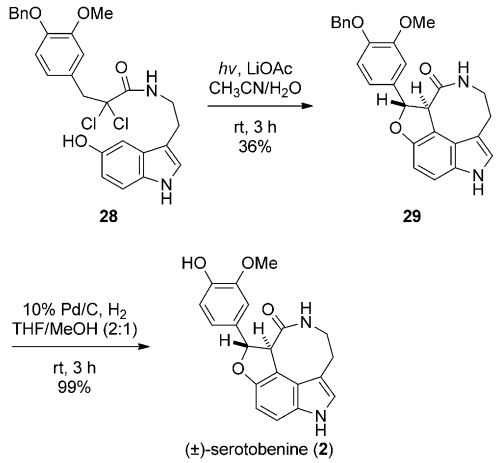



Scheme 5. Synthesis of (±)-decursivine.

presence of NaOAc and MeCN, there is no evidence of formation of the terminal double bond, which is the key structural feature of the product **13**. Instead, the natural product decursivine **1** was isolated as the sole product in 15% yield. This result indicated that an unexpected Witkop photocyclization/elimination/addition cascade reaction occurred and the cascade reaction produced the required *trans* stereochemistry of the dihydrobenzofuran. Although exactly how the addition reaction occurred was not clear initially, the cascade sequence did streamline the synthesis and shorten the synthetic route. We quickly carried out optimization of the newly discovered cascade reaction and found that both solvent and salt played an important role in this cascade sequence (see the Supporting Information). Under the optimized reaction conditions ($Li_2CO_3$, MeCN/$H_2O$ (10:1)), compound **15** was converted to the desired product **1** in 40% yield. Since it is known that the $Li^+$ ion facilitates organic photochemical reactions, it seems that $Li_2CO_3$ acted as a special salt rather than a base (see below).[24,19a] Considering that the yields of the Witkop procedure rarely exceed 50%, this result indicated the cascade Witkop photocyclization/elimination/addition sequence proceeded relatively well.

Thus, we achieved the total synthesis of decursivine (**1**) in only five steps from commercially available starting materials. The overall yield was 19% after two column chromatography purifications. Moreover, no protecting group was used. Therefore, our synthesis represents a substantial improvement over the previously reported ones.[6]

To demonstrate the utility of the developed cascade sequence further, a total synthesis of the natural product serotobenine (**2**) was performed as well (Scheme 6). The precursor **28** was prepared following the same synthetic Scheme as described for compound **15**. Upon irradiation of **28** under the optimized reaction conditions ($Li_2CO_3$, MeCN/$H_2O$ (10:1)), the desired product **29**, a known benzyl ether of serotobenine, was obtained albeit only in 5% yield. The reaction conditions were further optimized. Quickly, we found that the choice of salt was critical. Of the salts tested, LiOAc was the most efficient and the desired product **2** was obtained in 36% yield using LiOAc as the salt. According to the protocol reported by Fukuyama and co-workers, removal of the benzyl ether under hydrogenolysis condition yielded (±)-serotobenine (**2**), whose spectral data are in accord with those described in the literature.[3,4,11]

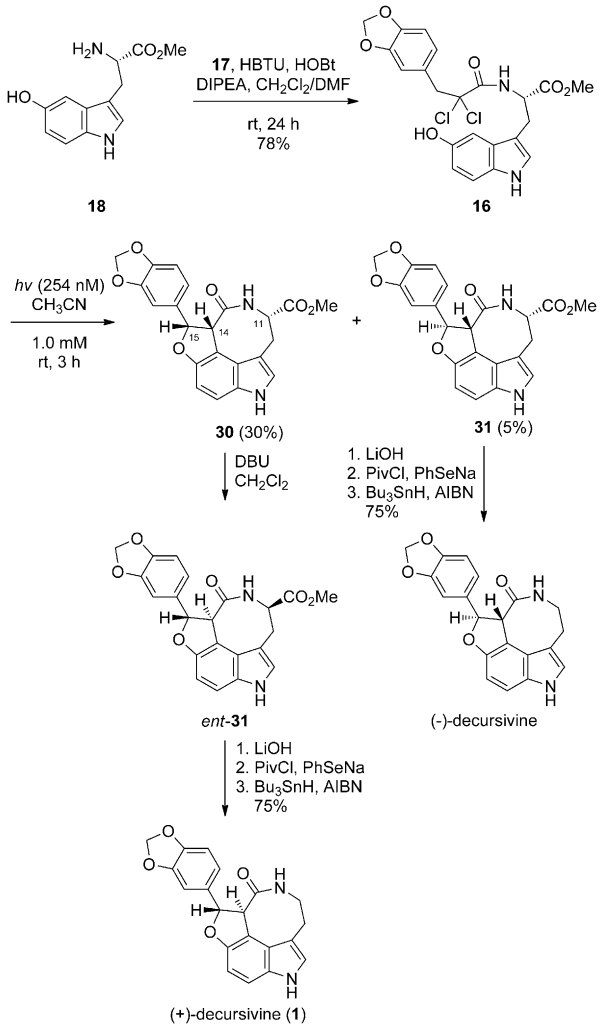



Scheme 6. Synthesis of (±)-serotobenine.

Our total synthesis of serotobenine (**2**) was achieved in only eight steps from commercially available starting materials in 14% overall yield, which also represents a substantial improvement over the previously reported synthesis.[11]

**Total synthesis of (+)- and (−)-decursivine**: Having accomplished the total synthesis of decursivine racemate in a substantially improved way, we turned our attention to the synthesis of the enantiopure decursivine (Scheme 7).

The precursor **16** was prepared by coupling amine **18** with acid **17**. Unexpectedly, irradiation of **16** under a variety of reaction conditions provided only trace amount of the de-




Scheme 7. Synthesis of (+)- and (−)-decursivine.

sired product **31**. Subsequently, a variety of conditions (solvents, salts, concentration, and wavelength) were further screened for the photocyclization reaction. In this case, we found that the irradiation wavelength played an important role. Irradiation of a solution of **16** (1.0 mM) at 254 nm in $CH_3CN$ yielded the *cis* product **30** (30% yield) and the *trans* product **31** (5% yield), which were readily separated by column chromatography. The NMR data of our synthesized product **31** was identical to those reported by Li.[9] Thus the stereochemistry of **31** was assigned as *trans*. Our synthesized compound **31** had an optical rotation of $[\alpha]_D^{24} = -201$, ($c = 1.0$ in $CHCl_3$), but the optical rotation reported in the literature is $[\alpha]_D^{24} = +150$, [9] ($c = 1.0$ in $CHCl_3$), indicating that our compound could be the enantiomer of the compound prepared by Li.[9] Removal of the methoxycarbonyl group of **31**, which should not affect the chiral centers at C14 and C15, led to the formation of (−)-decursivine. This indicated that the configurations of C14 and C15 in our synthesized product **31** are the same as that in (−)-decursivine.

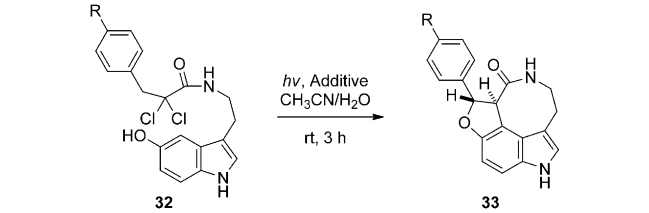
The relative conformation of the *cis* product **30** was deduced by the NOESY spectrum, which showed strong enhancement between the C14 and C15 protons. However, the absolute configurations at C14 and C15 were not known. We thought that *cis*-dihydrobenzofuran **30** could be epimerized under basic conditions to the more stable *trans*-dihydrobenzofuran, which may facilitate the identification of the configurations. Treatment of **30** with DBU in $CH_2Cl_2$ provided a compound that showed identical $R_f$ values on TLC and NMR spectra with **31**. Moreover, the optical rotation ($[\alpha]_D^{24} = +198$, $c = 1.0$ in $CHCl_3$) of the epimerized product of **30** was essentially the same in absolute value as that of **31** but in the opposite direction. These data clearly indicated that the epimerized product was *ent*-**31**. It is unlikely that C15 would epimerize and both C14 and C11 could easily epimerize under our conditions. All these considerations confirmed the structure of our obtained **30**. According to the protocol reported by Li,[9] compound **31** and *ent*-**31** were readily converted to (+)- and (−)-decursivine in a three-step sequence.

The spectra ($^1$H NMR, $^{13}$C NMR, and HRMS) of the synthesized (+)- and (−)-decursivine are in accord with those described in the literature.[2,6,9] However, there are small differences in the optical rotation.[2] Our synthesized (+)-decursivine showed an optical rotation of $[\alpha]_D^{23} = +224$, ($c = 0.02$ in $CH_3OH$), but the literature[2] value for the natural (+)-decursivine is $[\alpha]_D^{20} = +299$, ($c = 0.02$ in $CH_3OH$) and that of the synthesized one[9] is $[\alpha]_D^{23} = +283$, ($c = 0.02$ in $CH_3OH$). Our synthesized (−)-decursivine showed an optical rotation of $[\alpha]_D^{23} = -224$, ($c = 0.02$ in $CH_3OH$). To explain the lower absolute values of optical rotation of our synthesized (+)- and (−)-decursivine, their enantiomeric excesses were determined by chiral HPLC and the results showed that the enantiomeric excesses of synthesized (+)- and (−)-decursivine were both more than 97% (see the Supporting Information). Therefore, the total synthesis of (+)-decursivine (**1**) was achieved in only nine steps with 10% overall yield from commercially available starting materials.

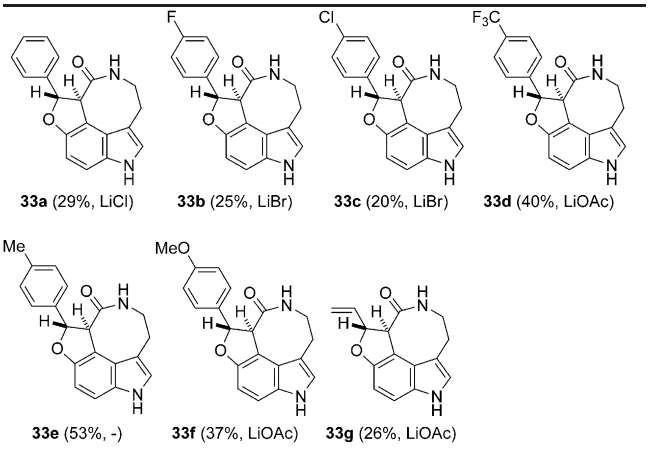
**The scope of the cascade sequence**: The exciting potential of the Witkop photocyclization/elimination/addition cascade sequence was exemplified in the synthesis of decursivine. Differences in the final products after photocyclization of different precursors were observed. For example, compounds **15**, **16**, and **28** formed the dihydrobenzofuran ring in the product after photocyclization, but compound **23** only provided α,β-unsaturated lactam. It seems that the substituents on the dichloroacetyl moiety affected the products. To obtain a clearer picture of the effects of dichloroacetyl moiety on the reaction products, various chloroacetyl serotonin with benzyl, allyl, and aliphatic substitutions were synthesized and examined.

The electronic contributions of substituents on the benzene ring were firstly examined (Table 1). The cascade reaction underwent smoothly for all of the tested substrates with

Table 1. Scope of the cascade sequence.[a]



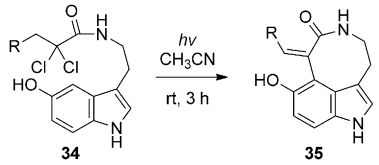

Product (Yield [%],[b] additive)

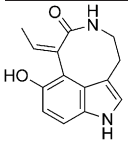
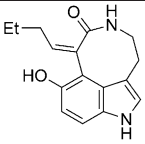
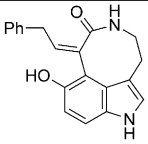
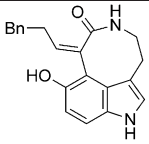



[a] General reaction conditions: concentration = 0.005 M, irradiation with 300 W high-pressure mercury lamp under argon atmosphere. [b] Yield of the isolated product.

electron-neutral (compound **32a**), electron-withdrawing (compounds **32b–32d**), and electron-donating (compounds **32e** and **32f**) groups, providing the corresponding analogues of decursivine. These results indicated that the electronic factors of the phenyl moiety did not affect the reactivity of this transformation. Interestingly, compound **32g** was also converted to dihydrobenzofuran **33g**. However, it is should be stressed that the reaction conditions for each compound needed to be optimized to obtain a reasonable yield.

Table 2. Scope of the cascade sequence.[a]

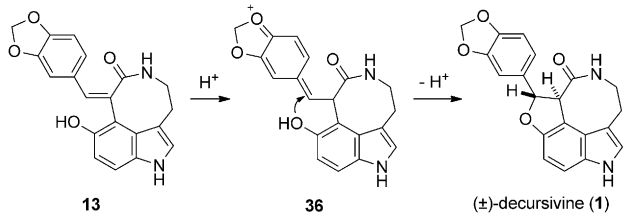



| Product (Yield [%])[b] | | | |
|---|---|---|---|
|  |  |  |  |
| **35a** (44%) | **35b** (50%) | **35c** (56%) | **35d** (20%) |

[a] General reaction conditions: concentration = 0.005 M, irradiation with 300 W high-pressure mercury lamp under argon atmosphere. [b] Yield of the isolated product.

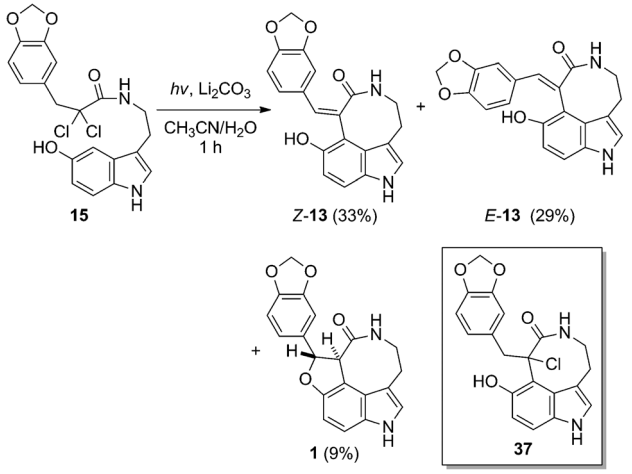
The substrates with different aliphatic substituents were examined next (Table 2). However, all of the tested substrates (**34**) provided the α,β-unsaturated lactams (**35**) as the sole product. It is noteworthy that only the *Z* isomer **35** was observed. These results clearly indicated that the products depended on the substituents on the dichloroacetyl moiety.

**Mechanistic insights**: With the initial investigations and scope exploration complete, differences in the final products after photocyclization of different precursors were observed. To explain these experiment phenomena, a comprehensive mechanistic understanding was sought. It is accepted that the compound **15** could be converted to **13** through a Witkop photocyclization/elimination sequence. However, it was still unclear how the final cyclization reaction happened. We previously proposed that the mechanism of the last cyclization step involves an unusual Michael addition.[8] However, it would be a 5-*endo*-*trig*, and therefore violates Baldwin's rules.[25] Mascal proposed that the HCl, liberated in the cascade reaction, mediates the ring-closure (Scheme 8).[7] However, it is known that the rigid methylenedioxy substituent on the phenyl ring in compounds such as **13** does not allow complete orbital overlap between the lone pairs of electrons on oxygen and the π-system of the phenyl group.[26] It does not agree with our observations in Table 2, in which the electron-neutral and electron-deficient phenyl and even olefin substrates provide the cyclization products. There are indeed reports that acid could mediate the cyclization, however, it needs to be a relatively strong acid.[20,27]




Scheme 8. The mechanism proposed by the group of Mascal.[7]

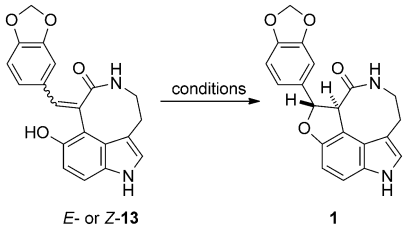
To gain insight into the mechanism of this cascade reaction, the separation of reaction intermediates such as **13** and **37** was firstly performed and the substrate **15** was used as model compound (Scheme 9). Fortunately, irradiation of **15** under the optimized reaction conditions for 1 hour yielded a mixture of the natural product **1** (9% yield), the desired *Z* isomer **13** (33% yield) and the *E* isomer **13** (29% yield). However, the intermediate **37** was never obtained.




Scheme 9. Separation of the reaction intermediates.

With the critical intermediate **13** in hand, a series of control experiments were performed (Table 3). Both *Z* and *E* **13** were individually subjected to the optimized reaction conditions, which provided the desired product **1** in 53% yield (Table 3, entry 1). It was also observed that the *Z* and *E* **13** could be isomerized during the reaction conditions.

Table 3. Control experiments.




| Entry | Conditions[a] | Yield[b] |
|---|---|---|
| 1 | *hv*, $Li_2CO_3$, $CH_3CN/H_2O$ (10:1) | 53 |
| 2 | *hv*, $CH_3CN/H_2O$ (10:1) | 54 |
| 3 | *hv*, $CH_3CN$ | 52 |
| 4 | $Li_2CO_3$, $CH_3CN/H_2O$ (10:1) | N.R |
| 5 | HCl (40 equiv), $CH_3CN$ | N.R |
| 6 | $BF_3{\cdot}Et_2O$ (15 equiv), $CH_2Cl_2$ | N.R |
| 7 | *hv* (254 nm), $CH_3CN$ | 45 |

[a] Concentration = 0.005 M, irradiation with 300 W high-pressure mercury lamp under argon atmosphere for 3 h. [b] Yield of the isolated product. N.R = no reaction.

These results confirmed that the olefin **13** is an intermediate of this cascade reaction. Further control experiments showed that both $Li_2CO_3$ and $H_2O$ were not necessary for the conversion of **13** to **1** (Table 3, entries 2 and 3). These results indicated that $Li_2CO_3$ and water only played an important role in the Witkop photocyclization step. The reaction did not occur in the dark, which demonstrated that the reaction was indeed promoted by photochemistry (Table 3, entry 4). When compound **13** was treated with 40 equiv of HCl or 15 equiv of $BF_3$•$Et_2O$, no reaction occurred (Table 3, entries 5 and 6). Since only 2 equiv of HCl would be liberated in the cascade reaction, it is unlikely that the liberated HCl mediates the ring-closure.

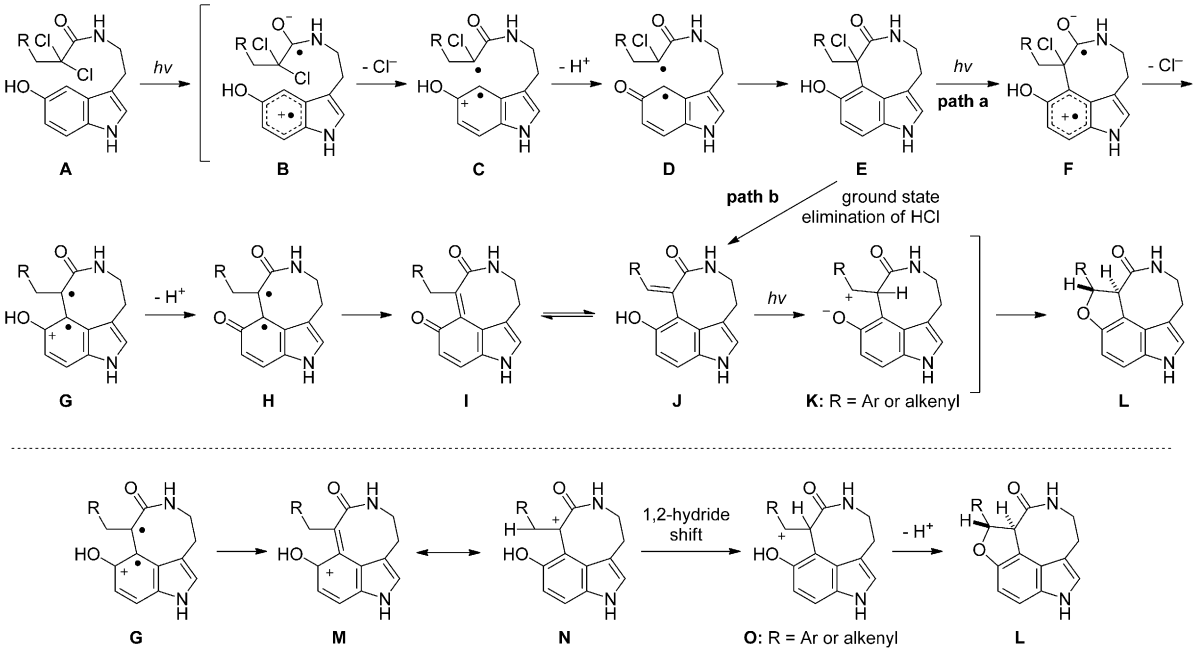
It is known that different reactivity exhibits between the ground state and the excited state. In fact, it was reported that dihydrobenzofurans could be formed from *o*-hydroxystyrene in photolysis, although it was sensitive to the structure of *o*-hydroxystyrene.[28] Therefore, it appears reasonable that the last cyclization step in the cascade sequence is mediated by photochemistry.

Based on the previous studies[17] and our current experimental results, a mechanistic pathway is proposed (Scheme 10). A single-electron transfer from the excited state of the indole chromophore to the chlorocarbonyl moiety causes dissociation of the C–Cl bond, leading to the formation of a diradical cation intermediate **C**. Intermediate **C** rapidly loses a proton to form intermediate **D**, which is then regioselectively cyclized to form intermediate **E**. Excitation of **E** by a photon provides the enone product **I**, which is then converted to **J** through a 1,5-hydrogen shift. In addition, since the intermediate **E** might be extremely labile, owing to an indole and phenol ring-activation through loss of a chloride ion, the conversion of **E** to **J** through a ground state elimination of HCl is also possible. However, since it is known that the photoelimination of HCl of α-chloro amide can provide an α,β-unsaturated amide,[18a] the HCl elimination step might be also promoted under our photochemistry conditions. This step is likely the fast step of this cascade reaction, thus we cannot rule out any one of two pathways. The reaction stops at this stage when R is an aliphatic substituent. When R is a phenyl or olefin substituent, excitation of **J** by a photon allows the intramolecular transfer of hydrogen from the phenolic hydroxyl group to the α-carbon of the styrene, forming a relative stable cation **K** that leads to the final dihydrobenzofuran product. For the last step of cyclization to occur, it is critical the R group can provide resonance stabilization of the cation **K**.

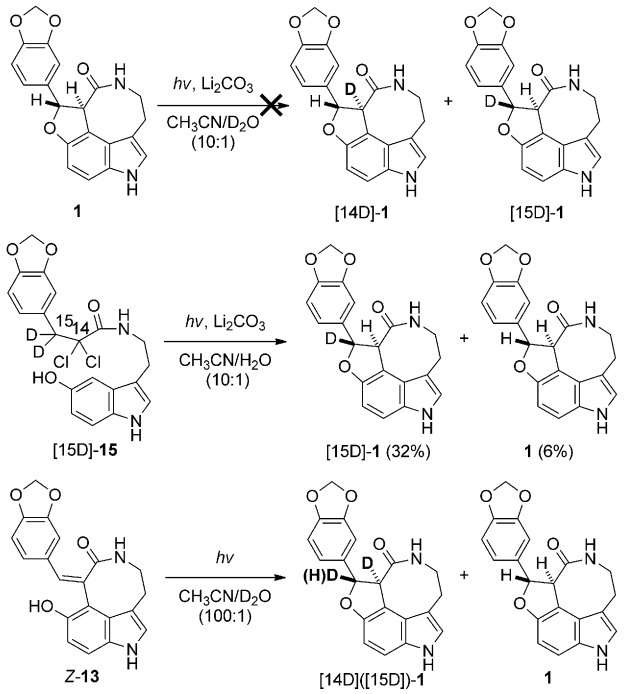
Alternatively, the diradical cation intermediate **G** could form the intermediate **M** or **N**, and then lose a proton to form **J** when the R group is an aliphatic substituent. When the R group is a phenyl or olefin substituent, intermediate **N** undergoes a 1,2-hydrogen shift to form the stable cation **O**, which then forms the dihydrobenzofuran ring and loses a proton. To determine which is the likely reaction process, experiments with deuterium-labeled compounds were performed (Scheme 11).

To rule out the possibility of H/D exchange at C14 and C15 of **1** under basic reaction conditions ($Li_2CO_3$, MeCN/$H_2O$ or $D_2O$), irradiation of **1** under the aforementioned reaction conditions was firstly performed (Scheme 11). However, it did not give any [14D]-**1** or [15D]-**1** products. This result indicated that H/D exchange at C14 and C15 of **1** did not occur under our reaction conditions.

Irradiation of compound [15D]-**15** under our optimized reaction conditions gave two products: [15D]-**1** (32% yield) and **1** (6% yield), demonstrating that there was no 1,2-hy-




Scheme 10. Mechanistic insights.




Scheme 11. Deuterium experiments.

drogen shift. This result is also in agreement with a previous statement that the indole radical cation (**C** and **G**) is quite unstable and rapidly loses a proton prior to the cyclization to form the neutral radical, which might be the reactive intermediary species.[29] The formation of **1** indicates that the interconversion between *o*-quinonemethide (**I**) and *o*-hydroxystyrene (**J**) must have taken place.

To demonstrate the intramolecular hydrogen-transfer from the phenolic hydroxyl group to the α-carbon of the styrene in **J** to form intermediate **K**, exchange of the hydroxyl proton of *Z*-**13** with deuterium oxide, followed by photocyclization of the resulting deuterated *Z*-**13**, was performed. As expected, [14D]([15D])-**1** was obtained as the main product, which demonstrates the proposed hydrogen transfer.[28] This is also the first time to obtain the experiment evidence that the dihydrobenzofuran ring is formed through an intramolecular protonation. The reaction products in the presence of deuterium oxide indicate again that the interconversion between *o*-quinonemethide (**I**) and *o*-hydroxystyrene (**J**) must have taken place.

## Conclusion

During our total synthesis of the antimalarial agent decursivine, we discovered a new cascade Witkop photocyclization/elimination/addition sequence, which enabled the expedient synthesis of racemic decursivine and serotobenine, enantiopure (+)- and (−)-decursivine, and a variety of decursivine analogues. The present syntheses represent the shortest and most efficient pathway for the total synthesis of decursivine and serotobenine to date. Based on the previous studies and our current experimental data, the reaction mechanism of the cascade sequence is proposed. Our syntheses demonstrate the power of cascade reactions in the construction of complex molecules. These studies are yet another example in which natural products explorations are catalyzing the discovery of new reactions.

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Total Synthesis

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**Total Synthesis of (+)- and (−)-Decursivine and (±)-Serotobenine through a Cascade Witkop Photocyclization/Elimination/Addition Sequence: Scope and Mechanistic Insights**

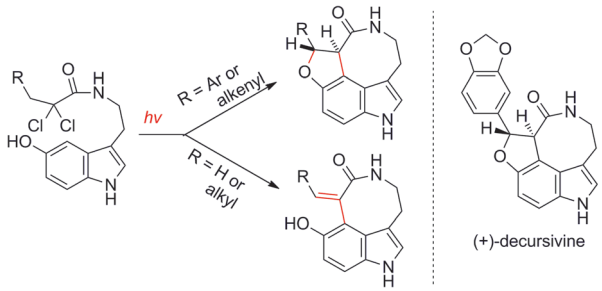


**Photo-mediated cascade reaction**: The total synthesis of enantiopure (+)- and (−)-decursivine and (±)-serotobenine was achieved through our developed cascade Witkop photocyclization/elimination/addition sequence (see scheme). The scope of the cascade sequence was investigated, and a variety of analogues of decursivine were synthesized. A rational mechanism for the cascade sequence was also proposed based on our current experimental results.