Decursivine

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Total Synthesis of (±)-Decursivine and (±)-Serotobenine: A Witkop Photocyclization/Elimination/O-Michael Addition Cascade Approach**

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The 'ideal' synthesis is pursued actively by organic chemists since it encompasses the ideas of atom, step, and redox economy.[1,2] Cascade reactions offer an attractive strategy for the synthesis of complicated natural products, especially when the cyclization is a biomimetic process.[3] Additionally, the avoidance of protecting groups is a major aspect of streamlining a synthesis.[4] With our ongoing interest in the study of indole alkaloids and the pursuit of the ideal synthesis,[5] we describe herein short and efficient total syntheses of the indole alkaloids (±)-decursivine (**1**) and (±)-serotobenine (**2**) that are facilitated by a cascade Witkop photocyclization/elimination/O-Michael addition sequence (Figure 1).

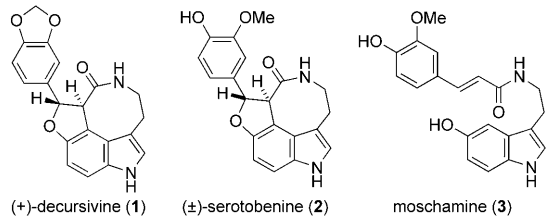
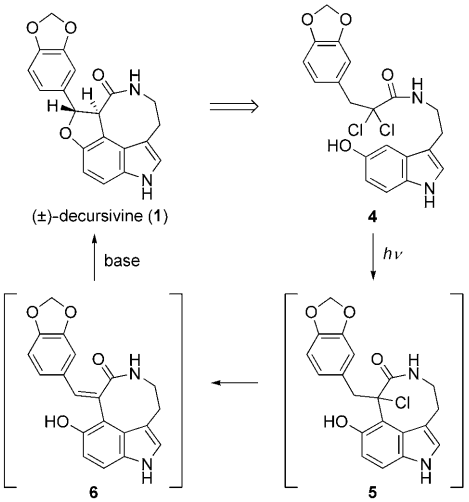


Figure 1. Structures of (+)-decursivine (**1**) and related alkaloids.

(+)-Decursivine (**1**), which was isolated from *Rhaphidophora decursiva* in 2002, showed antimalarial activity with IC_{50} values of 3.93 and 4.41 μg mL^{-1} against the D6 and W2 clones of *Plasmodium falciparum*, respectively.[6] During the isolation of (+)-decursivine, (±)-serotobenine (**2**) was also isolated from the leaf extract. However, unlike **1**, **2** exhibits no activity against *Plasmodium falciparum*. Furthermore, serotobenine exists as the racemic form in nature.[7] Biosynthetically, both **1** and **2** are derived from moschamine (**3**).[8] The unique structure of both decursivine and serotobenine contains a multicyclic structure involving an indole, a dihydrobenzofuran, and an eight-membered lactam that bridges the indole 3 and 4 positions. The prominent synthetic challenges are the sensitivity of the electron-rich indole to oxidation, the stereogenic centers on the dihydrobenzofuran, and the formation of the eight-membered lactam. Leduc and Kerr reported the first total synthesis of **1** in 18 linear steps and 3% overall yield, and Mascal et al. reported the four-step synthesis of **1** in 53% overall yield by using an approach similar to the one described herein.[9] Fukuyama and co-workers reported the total synthesis of (−)-serotobenine in 24 linear steps and 8% overall yield.[10]

The Witkop photocyclization of N-haloacetyl tryptophan derivatives can form the eight-membered lactam that bridges the indole 3 and 4 positions.[11,12] However, it has been employed only sporadically in natural product synthesis.[13] Furthermore, there are only two reports in which dichloroamide underwent photocyclization with subsequent elimination of HCl to give the α,β-unsaturated lactam, which is a Michael receptor;[13b,e] however no cascade reaction has been designed using this intermediate.

We envisioned that compound **4** could undergo the Witkop photocyclization/elimination sequence to provide α,β-unsaturated lactam **6**, which might undergo an intramolecular O-Michael addition in the presence of a base to produce **1** with the correct relative configuration, thus following the biosynthetic pathway (Scheme 1). If this



Scheme 1. Retrosynthetic analysis of (±)-decursivine (**1**).

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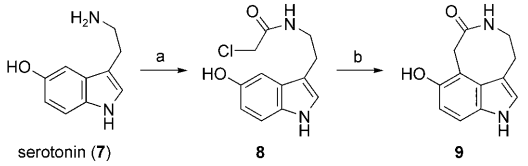
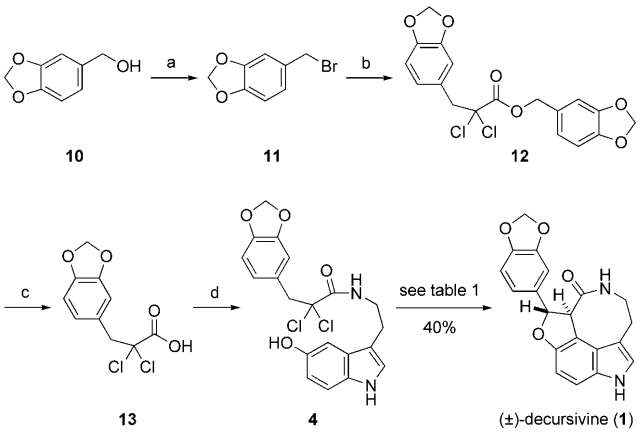
cascade reaction could be realized, it would streamline the synthesis and shorten the synthetic route.

To test this concept, we first investigated whether the free phenol could tolerate the reaction conditions. The simple compound **8** was prepared from serotonin (**7**; Scheme 2). When irradiated in THF/H_2O (5:1) in the presence of NaOAc, the chloroacetyl serotonin **8** was successfully converted into the desired product **9** in 34% yield (not optimized).[11b]



Scheme 2. Photocyclization of **8**. Reagents and conditions: a) $(ClCH_2CO)_2O$, Et_3N, CH_2Cl_2/DMF (3:1), 0°C→RT, 3 h, 80%; b) *hν*, NaOAc, THF/H_2O (5:1), RT, 6 h, 34%. DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

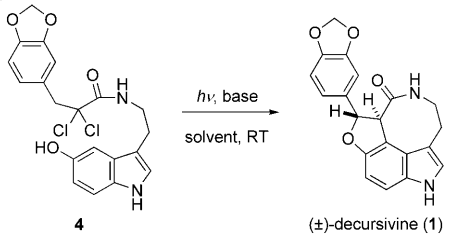
With the success of our model studies, we turned our attention to the total synthesis of **1**. The synthesis of the key intermediate **4** begins with the known compound **11** (Scheme 3), which is readily available from **10** in one step.[14] Reaction of **11** with Cl_3CO_2Na in CCl_4 and subsequent hydrolysis with NaOH provided acid **13**.[15] Coupling acid **13** with **7** using HBTU afforded the key intermediate **4** in 88% yield.



Scheme 3. Total synthesis of (±)-decursivine (**1**). Reagents and conditions: a) PBr_3, CH_2Cl_2, 0°C→RT, 3 h, 95%; b) Cl_3CCO_2Na, nBu_4NBr, CCl_4, 60°C, 24 h, 60%; c) NaOH, THF/H_2O (3:1), RT, 3 h, 95%; d) **7**, HBTU, HOBt, DIPEA, CH_2Cl_2/DMF (5:1), RT, 24 h, 88%. HBTU = 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, HOBt = *N*-hydroxybenzotriazole, DIPEA = diisopropylethyl amine

With compound **4** in hand, the crucial cascade reaction was next investigated, and some of the representative results are shown in Table 1. It was revealed that both the solvent and base played important roles in this cascade sequence. When

Table 1: Optimization of the reaction conditions.[a]



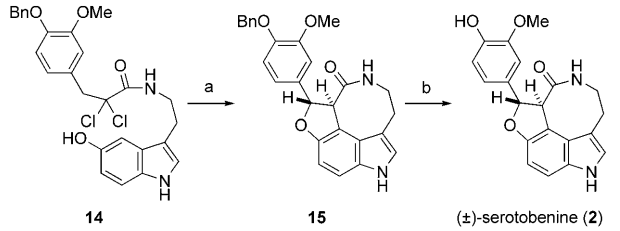
Entry	Base	Solvent	Yield [%][b]
1	NaOAc	THF/H_2O (5:1)	5
2	NaOAc	THF	0
3	NaOAc	CH_3CN/acetone (10:1)	5
4	NaOAc	CH_3CN	15
5	LiOAc	CH_3CN	0
6	Et_3N	CH_3CN	5
7	$NaHCO_3$	CH_3CN	5
8	Na_2CO_3	CH_3CN	8
9	Li_2CO_3	CH_3CN	30
10	Li_2CO_3	CH_3CN/H_2O (10:1)	40

[a] Reaction conditions: **4** (0.1 mmol), base (0.5 mmol), solvent (22 mL), RT, 3 h. [b] Yields of isolated products.

THF/H_2O (5:1) was used as solvent, the desired product **1** was obtained in only 5% yield (Table 1, entry 1). Changing the solvent to either THF or CH_3CN/acetone (10:1) gave similar results (entries 2 and 3). When CH_3CN was used as the solvent, **1** was obtained in 15% yield (entry 4). A variety of inorganic and organic bases were also examined in an attempt to increase the yield of **1** (entries 4–9). Li_2CO_3 proved to be superior to any other bases so far tested. Furthermore, the use of Li_2CO_3 in MeCN/H_2O (10:1) increased the yield of **1** to 40% (entry 10).

Importantly the cascade reaction provided the required *trans* stereochemistry of the dihydrofuran. Since the yields of the Witkop procedure rarely exceed 50%, the results of the reaction optimization (Table 1) indicate that the Witkop photocyclization/elimination/O-Michael addition sequence proceeded relatively well. The total synthesis of **1** was achieved in only five steps, using two column chromatography purifications, from commercially available starting materials. The overall yield was 19% and moreover, no protecting groups were used. Thus, this synthesis represents a substantial improvement over the previously reported syntheses.

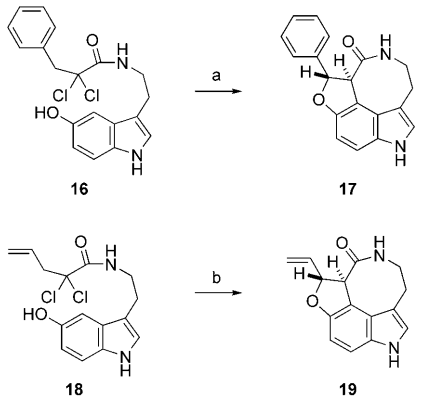
To further demonstrate the utility of the developed cascade sequence, the total synthesis of the natural product serotobenine (**2**) was performed as well (Scheme 4). The precursor **14** was prepared by using the same synthetic steps as described for compound **4**. Irradiation of **14** under the aforementioned optimized reaction conditions [Li_2CO_3, MeCN/H_2O (10:1)] gave the desired product **15**, that is, the known benzyl ether of serotobenine, in 5% yield. Therefore, the reaction conditions were additionally optimized. It was revealed that the choice of the base was again critical. Of the bases tested, LiOAc was the most efficient and afforded the desired product **15** in 36% yield. By using the protocol reported by Fukuyama and co-workers, removal of the benzyl ether by hydrogenolysis gave **2**, the characterization data of



Scheme 4. Total synthesis of (±)-serotobenine (**2**). Reagents and conditions: a) *hν*, LiOAc, CH_3CN/H_2O (5:1), RT, 3 h, 36%; b) H_2, 10% Pd/C, THF/MeOH (2:1), RT, 3 h, 99%. Bn = benzyl.

which are in agreement with those described in the literature.[7,10]

Finally, we wished to determine if the developed cascade sequence could be applied to the preparation of some simple analogues of **1**. As shown in Scheme 5, this goal was achieved by starting with both **16** and **18**, which were obtained through the same general sequence of steps as described above for **4**.



Scheme 5. Photocyclization of **16** and **18**. Reagents and conditions: a) *hν*, LiCl, CH_3CN/H_2O (5:1), RT, 3 h, 29%; b) *hν*, LiOAc, CH_3CN/H_2O (5:1), RT, 3 h, 26%.

Once again, the reaction conditions for each compound needed to be optimized to obtain an acceptable yield. These results clearly indicate that there is in fact no 'ideal' system, but that each reaction requires optimization.

In summary, we have developed short and direct routes to (±)-decursivine (**1**) and (±)-serotobenine (**2**). In addition to providing both natural products, the method can provide access to analogues, thus enabling a more comprehensive evaluation of their biochemical potential. The unique feature of the present synthesis is the use of a Witkop photocyclization/elimination/O-Michael addition cascade in a biomimetic manner. Moreover, protecting groups were not used, thus allowing an efficient five-step synthesis of the natural product **1** in 19% overall yield.

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