Decursivine

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Concise Photochemical Synthesis of the Antimalarial Indole Alkaloid Decursivine

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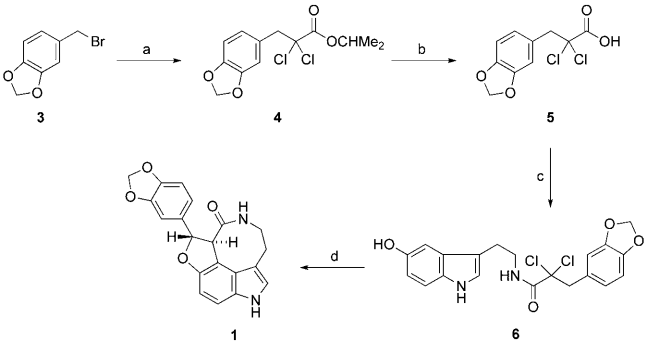
Malaria is among the most serious and persistent health hazards known to man, with over 200 million infections leading to approximately 1 million fatalities annually, more than 80% of which being in children under five.[1] It is for this reason that the development of simple routes to effective antimalarials is an urgent priority in the global health arena. Current therapies are based around derivatives of the sesquiterpene peroxide artemisinin[2] but evidence of resistance to this line of treatment is already being reported,[3] and the identification of new drug leads for the inhibition of malaria remains an active pursuit.

Decursivine (**1**) is an extracyclic indole alkaloid which shows activity (4.4 $\mu g\,mL^{-1}$) against the chloroquinine-resistant malaria parasite *Plasmodium falciparum*.[4] It was recently isolated from active extracts of *Rhaphidophora decursiva*, a perennial, evergreen vine native to Vietnam. Interestingly, its structure was found to be nearly identical to the known safflower alkaloid serotobenine (**2**).[5]

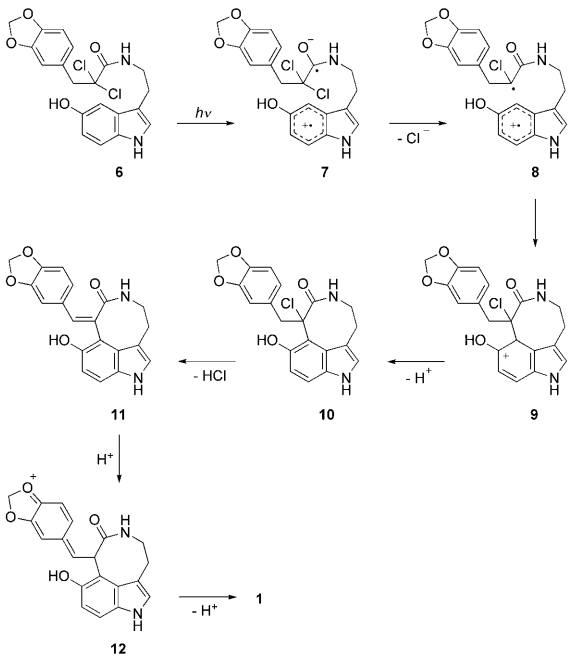
The only reported synthesis of **1** is a 20-step route from *p*-aminophenol.[6] A more recent synthesis of the closely related serotobenine (**2**) required 24 steps from 3-methyl-4-nitrophenol.[7] We report herein a synthesis of (±)-**1** in four steps from commercially available piperonyl bromide **3**. A synthesis similar to the one reported herein is being concurrently reported by Jia and co-workers.[8]

Our synthetic approach is described in Scheme 1. Thus, the lithium enolate of isopropyl dichloroacetate is generated using lithium hexamethyldisilazide (LHMDS) and alkylated with bromide **3** to give the dihydrocinnamate derivative **4** in good yield. Although the corresponding methyl ester can also be used here, the reaction turns out to be less reliable because of the frequent observation of the competing Claisen product. The hydrolysis of **4** into **5** is facile, but initial attempts to couple this sterically hindered acid to serotonin using dicyclohexylcarbodiimide (DCC) were unsuccessful. Ultimately, it was found that diphenylphosphoryl azide (DPPA) could be used to promote the reaction in high yield. The key transformation in this synthesis is the photochemically induced cyclization of dihaloamide **6** to the product **1**. In fact, this step comprises a remarkable cascade of events as depicted in Scheme 2.

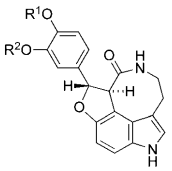


Scheme 1. Reagents and conditions: a) $Cl_2CHCO_2CHMe_2$, LHMDS, THF, 90%; b) KOH, H_2O, MeOH, 98%; c) serotonin, DPPA, collidine, DMF, 84%; d) *hν*, MeCN, 72%.

The process by which the initial ring closure takes place is a precedented but little used reaction called the Witkop cyclization.[9] It has been previously exploited only to a very limited extent for synthetic purposes. Thus, Moody and co-



Scheme 2. Mechanistic interpretation of the conversion of **6** into **1**.



1, $R^1=R^2=-CH_2-$
2, $R^1=H$, $R^2=CH_3$

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workers used it in a key step in the construction of the tumor-promoting alkaloid indolactam V,[10] and likewise Feldman and co-workers in an approach to a dragmacidin E fragment.[11]

Mechanistically, the reaction involves the photoionization of the electron-rich indole ring and electron capture by the amide carbonyl group. The same kind of cyclization reaction has been reported for gly–trp and ala–trp,[12] and may also be implicated in the photodenaturation of tryptophan-containing peptides.[13] The resulting intermediate **7** loses chloride to become diradical cation **8**, which recombines and rearomatizes to **10**. Elimination of HCl gives **11** which is protonated to quinone methide intermediate **12**. This allows for a 5-*exo*-trig cyclization, which proceeds to **1** exclusively with the correct relative configuration.[14]

The electron-transfer mechanism and intermediacy of radical cations in the Witkop cyclization have been supported by fluorescence quenching, flash photolysis, and solvent effect studies. Early work in this area by Hammond and co-workers dealt with the efficient quenching of indole fluorescence by haloacetamides, an effect that was not observed in the absence of the halogen.[15] The absence of low-lying singlet states in the quencher precluded simple excitation transfer, and detailed photochemical and theoretical studies on model compounds led to a mechanistic interpretation involving diradical cation intermediates of type **8**.[16,17] In a tour de force analysis of the reaction, the cyclic product distribution resulting from the irradiation of each of the seven regioisomers of chloroacetamidoethylindole was correlated with the singly occupied molecular orbital coefficients of the indole radical.[18] An intuitive assignment of the positive charge of the indole radical cation to positions stabilized by N1 (C2, C5, and C7) leads to the conclusion that the odd electron will preferentially reside at C3, C4, and C6, and this has been substantiated by computational modeling, which predicts a higher spin density at C4 than the alternative cyclization site C2 at all levels of theory.[19]

As regards the other steps in Scheme 2, the electronic reorganization required between **7** and **8** can be readily envisaged to proceed through an oxirane intermediate, but there is no direct evidence for this. The elimination of HCl from **10** is a reaction that is precedented in the photolysis of the 2,2-dichloro-3-methylbutanamide of tryptophan methyl ester,[10] leading to an isopropylidene-substituted lactam analogous to **11**. Since **11** cannot directly cyclize to **1**, it appears reasonable to propose that the liberated HCl mediates the ring closure as shown to conclude the synthesis. A related cyclization route was explored in the paper which described the synthesis of **2**.[7]

An exceptionally useful aspect of using Witkop chemistry in the synthesis of 3,4-bridged indoles such as **1** is that it invokes excited-state reactivity, leading to regiochemical outcomes that would not be expected in the ground state, for example the closure of an eight-membered ring to a normally inert ring atom (i.e. indole C4) in preference to the closure of a seven-membered ring to a normally reactive one (i.e. indole C2). Looking at the reaction from a mechanistic perspective, electron acceptors other than the haloamide function could also be envisaged, potentially leading to facile annulation of other ring systems onto indole. For example, a photochemical ring closure of a pendant iminium function onto an electron-rich aromatic ring has been described and was likewise shown to proceed through a diradical cation pathway.[20]

Finally, we note that the step which determines the absolute configuration in this synthesis is the protonation of **11** to give **12**. The absolute configuration of natural (+)-**1** has not been reported, but the configuration of the nearly identical (−)-**2** is known to be *R*,*R*.[7] It would be interesting to determine whether the presence of a chiral strong acid during the irradiation would influence the chiral outcome of the photocyclization reaction. We look forward to investigating this and other applications of the Witkop cyclization in ongoing work.

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