Total Synthesis of (±)-Decursivine *via* BINOL-Phosphoric Acid Catalyzed Tandem Oxidative Cyclization

Prakash T. Parvatkar

Northeastern University

Eugene S. Smotkin

Northeastern University

Roman Manetsch (✉ r.manetsch@northeastern.edu)

Northeastern University

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Abstract

Synthesis of tetracyclic indole alkaloid ($\pm$)-decursivine was accomplished through BINOL-phosphoric acid catalyzed tandem oxidative cyclization as a key step with hypervalent bis(trifluoroacetoxy)iodo)benzene (PIFA) as an oxidizing agent. This represents one of the shortest and highest yielding route for the synthesis of ($\pm$)-decursivine from readily available starting materials.

Introduction

Decursivine **1**, an indole alkaloid, was isolated in optically active form from the leaves and stems of *Rhaphidophora decursiva* Schott (*Araceae*) by Fong's group¹ in 2002. Decursivine is structurally related to serotobenine **2** (isolated as a racemic mixture in 1985 by Sato *et al.*)² with a unique tetracyclic framework containing a *trans*-dihydrobenzofuran, an indole, and an eight-membered lactam that bridges the indole 3- and 4-positions (Figure 1). Decursivine **1** exhibits antimalarial activity¹ against the D6 and W2 isolates of *Plasmodium falciparum* with IC₅₀ values of 3.93 and 4.41 μ g/mL respectively, whereas serotobenine **2** exhibits no activity against *Plasmodium falciparum*.

Owing to its novel structural features and potent antimalarial activity, decursivine has been the target of synthesis over the last decade.³⁻¹¹ The first total synthesis of ($\pm$)-decursivine was reported in 2007 by Kerr and co-workers⁴ in 19 steps using Diels-Alder/Plieninger indolization as the key steps with 3.7% overall yield. Later in 2011, the two groups of Jia⁵ and Mascal⁶ independently developed at the same time a 4 steps total synthesis of ($\pm$)-decursivine through cascade photocyclization/elimination/*O*-Michael addition protocol with overall yields of 47.6% and 53.3% respectively. Further in 2013, Jia's group⁷ extended this cascade by a Witkop photocyclization approach wherein (+)- and (-)-decursivine were obtained with overall yield of 9.5% and 1.6% in 9 and 8 steps, respectively. First asymmetric total synthesis of (+)-decursivine was developed in 2011 by Li and co-workers⁸ in 11 steps that involve intramolecular [3+2] cycloaddition as the main step with an overall yield of 16.7%. In 2014, Jia's group⁹ reported the synthesis of ($\pm$)-decursivine *via* cascade C-H activation/oxidation approach in 4 steps with an overall yield of 19.3%. Subsequently in 2015, Jia's group¹⁰ broadened this cascade approach (C-H activation/oxidation) to synthesize (-)-decursivine in 11 steps with 6.5% overall yield. Recently in 2016, Xia and co-workers¹¹ reported the total synthesis of (+)-decursivine in 11 steps *via* iron-catalyzed oxidative radical coupling protocol with an overall yield of 17.7%.

Results And Discussion

In continuation of our work towards antimalarial heterocyclic compounds¹²⁻¹⁵ and indole-containing natural products,¹⁶⁻¹⁹ we report a 5 steps total synthesis of ($\pm$)-decursivine, an antimalarial indole alkaloid from inexpensive and commercially available simple starting materials. Our retrosynthetic plan is illustrated in figure 2. We envisaged that, decursivine **1** could be obtained from **3** *via* tandem oxidative

cyclization, which in turn could be prepared by simple coupling reaction from readily and inexpensively available starting materials serotonin hydrochloride **4** and 3,4-(methylenedioxy)cinnamic acid **5**.

Our initial efforts towards the synthesis of (±)-decursivine **1** is described in figure 3. Coupling of serotonin hydrochloride **4** with 3,4-(methylenedioxy)cinnamic acid **5** using HBTU afforded key intermediate **3** (Figure 3). Direct conversion of **3** into **1** *via* tandem oxidative cyclization (oxidation through single electron transfer followed by cycloaddition) using photochemistry and electrochemistry approaches besides different oxidizing agents under varying reaction conditions was unsuccessful and most of the time, **3** underwent decomposition (Table 1).

Sr. No.	Reaction condition	Time (h)	Yield of 1 (%)
1	Ru(bpz) ₃ (PF ₆) ₂ (0.1 equiv), (NH ₄) ₂ S ₂ O ₈ (2 equiv), CH ₃ CN, Ar, blue LED, rt	18	decomposed
2	Acridinium (0.1 equiv), TBHP (2 equiv), CH ₃ CN, Ar, blue LED, rt	48	decomposed
3	CAN (2.5 equiv), CH ₃ CN, Ar, 0 °C	2	decomposed
4	Mn(OAc) ₃ ·2H ₂ O (4 equiv), CH ₃ CN, Ar, reflux	5	decomposed
5 ^a	Glassy carbon anode, Glassy carbon cathode, 0.1M LiClO ₄ , 1.25V	18	-
6 ^a	Platinum anode, Glassy carbon cathode, 0.1M, LiClO ₄ , 1.25V	10	-

^aPassivation of electrode observed.

Table 1. Tandem oxidative cyclization of compound **3**

These failures motivated us to protect the indole and amide -NH (Figure 4). First, hydroxy group of **3** was protected using TBSCl to give OTBS-protected compound **6**. Indole and amide -NH was then protected by refluxing **6** and Boc₂O in THF in presence of DMAP to provide fully protected compound **7**. Deprotection of silyl group of compound **7** by treatment with TBAF yielded hydroxy derivative **8**. Once compound **8** was in our hand, we investigated tandem oxidative cyclization under various reaction conditions as shown in Table 2.

Sr. No.	Reaction condition	Time (h)	Yield ^a of 1 (%)
1	I ₂ (0.1 equiv), TBHP (2 equiv), EtOH, Ar, reflux	48	no reaction
2	CAN (2.5 equiv), CH ₃ CN, Ar, 0 °C	2	decomposed
3	Mn(OAc) ₃ ·2H ₂ O (4 equiv), CH ₃ CN, Ar, reflux	5	decomposed
4	KHMDS (1.05 equiv), THF, Ar, 0 °C to rt	2	decomposed
5	Ru(bpz) ₃ (PF ₆) ₂ (0.1 equiv), (NH ₄) ₂ S ₂ O ₈ (2 equiv), CH ₃ CN, Ar, blue LED, rt	24	decomposed
6	[Ir(dtbbpy)(ppy) ₂](PF ₆) (0.1 equiv), BrCCl ₃ (2 equiv), CH ₃ CN, Ar, blue LED, rt	36	decomposed
7	Acridinium (0.1 equiv), TBHP (2 equiv), CH ₃ CN, Ar, blue LED, rt	48	decomposed
8	PIFA (1.2 equiv), HFIP, Ar, rt	6	47
9	PIFA (1.2 equiv), H ₃ PO ₄ (0.1 equiv), HFIP, Ar, rt	4	trace
10	PIFA (1.2 equiv), (±)-BINOL phosphoric acid (0.05 equiv), HFIP, Ar, rt	3	74

^aIsolated yield after column chromatography

Table 2. Tandem oxidative cyclization of compound **8**

Oxidation of Boc-protected compound **8** through single electron transfer followed by cyclization using different oxidizing agents or photochemistry approaches (entries 1-6), did not yield the product, instead the compound **8** underwent decomposition. We then turned our attention towards two electron oxidation/cyclization approach using hypervalent iodine reagent. In the literature, hypervalent iodine have been used for the oxidative [3+2] cycloaddition of various phenols and styrenes to give 2,3-dihydrobenzofuran derivatives.²⁰⁻²⁴ So, we treated compound **8** with hypervalent iodine reagent bis(trifluoroacetoxy)iodo)benzene (PIFA), and the product **1** was obtained in 48% yield (entry 7). Moderate yield of the product could be due to the decomposition of some of the *in situ* formed quinone intermediate before undergoing the cycloaddition. Masson's group²⁵ recently reported the use of chiral phosphoric acid to catalyze the intermolecular oxidative [3+2] cycloaddition for the asymmetric synthesis of 3-aminodihydrobenzofurans. With an idea of stabilizing the *in situ* formed quinone intermediate²⁵ *via* hydrogen bonding, we first attempted the reaction with H₃PO₄ (entry 8) to catalyze the [3+2] cycloaddition. Under these conditions, the reaction was sluggish forming trace amount of product, which was only observed by LC-MS. Using (±)-BINOL phosphoric acid (entry 9), the reaction was faster and the product was obtained in higher yield. The probable mechanism for the BINOL phosphoric acid catalyzed [3+2] cycloaddition is shown in figure 5.

PIFA oxidizes **8** to form quinone intermediate **9** which may be stabilized by BINOL phosphoric acid through hydrogen bonding²⁵ to give adduct **10**. Intramolecular cyclization of adduct **10** forms eight-membered lactam intermediate **11** that, loses a proton to generate phenolic species **12**. During this

process, BINOL phosphoric acid is released for the next catalytic cycle. Finally, annulation of **12** will lead to the formation of 2,3-dihydrobenzofuran containing compound **13** (*N*-Boc-protected decursivine).

Next, to induce chirality to the molecule, we investigated chiral BINOL phosphoric acid catalyst as shown in table 3. We used (*S*)-BINOL phosphoric acid (entry 1) and the bulky (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-BINOL phosphoric acid (entry 2) to induce chirality during oxidative cyclization. Unfortunately, no or negligible (< 2%) enantioselectivity was observed and the racemic product is obtained in 74% and 67% yield respectively.

Sr. No.	Reaction condition	Yield ^a (%)	ee ^b (%)
1	PIFA (1.2 equiv), (<i>S</i>)-BINOL Phosphoric acid (0.05 equiv), HFIP, Ar, rt, 3 h	74	-
2	PIFA (1.2 equiv), (<i>R</i>)-3,3'-bis(2,4,6-triisopropylphenyl)-BINOL phosphoric acid (0.05 equiv), HFIP, Ar, rt, 3 h	67	< 2%

^aIsolated yield after column chromatography, ^bDetermined by HPLC

Table 3. Attempted asymmetric synthesis of decursivine using chiral BINOL phosphoric acid

Conclusion

In conclusion, we have developed a short total synthesis of (±)-decursivine, an antimalarial natural product *via* cascade oxidative cyclization using PIFA as an oxidizing agent and (±)-BINOL phosphoric acid as a catalyst with a good overall yield of 43.8%.

Methods

General remarks

Reagents and solvents were purchased from commercial suppliers (Fisher Scientific {Hampton, New Hampshire, USA}, Sigma-Aldrich {St. Louis, Missouri, USA}, Strem Chemicals {Newburyport, Massachusetts, USA} and TCI America {Portland, Oregon, USA}) and used without further purification unless otherwise stated. Melting points were recorded on MEL-TEMP laboratory device. ¹H and ¹³C NMR

spectra were recorded at ambient temperature on a Varian Mercury NMR spectrometer (Palo Alto, California, USA) operating at 400 MHz (^1H NMR) and 100 MHz (^{13}C NMR) in the solvent indicated with the signal of the residual solvent (Chloroform- d δ 7.26 ppm or Methanol- d_4 δ 3.31 ppm or Pyridine- d_5 δ 8.74, 7.58, 7.22 ppm) as internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) and integration. Thin-layer chromatography (TLC) was performed with silica gel 60 F₂₅₄ pre-coated plates and visualized with exposure to UV light (254 nm) or by iodine staining. Flash chromatography was performed on Biotage (Model: Isolera, Sweden). ESI-MS were recorded on Agilent Technologies 6120 Quadrupole spectrometer (Santa Clara, California, USA). HRMS were recorded on MDS Analytical Technologies AB SCIEX TOF/TOF 5800 spectrometer (Sunnyvale, California, USA). Electrochemical Experiments were performed with an EZstat Pro potentiostat galvanostat (NuVant Systems, Crown Point, IN, USA).

Synthesis of compound 3

Serotonine hydrochloride **4** (306 mg, 1.44 mmol) and 3,4-(methylenedioxy)cinnamic acid **5** (276 mg, 1.44 mmol) was dissolved in DMF (10 mL). To this solution was added DIPEA (375 μL , 2.15 mmol), HOBt $\cdot$ 3H₂O (326 mg, 1.72 mmol) and HBTU (655 mg, 1.72 mmol) and stirred at room temperature for 24 hours. The reaction mixture was diluted with EtOAc (50 mL) and washed with saturated aqueous NH₄Cl, H₂O and brine. The organic phase was dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. Crude product was purified using Flash chromatography on Biotage Snap Cartridge (KP-Sil 25 g) using gradient solvent system (40% to 90% ethyl acetate in hexanes) to give product **3** (434 mg, 86% yield). White solid. Mp 96-98 °C. R_f = 0.33 (70% ethyl acetate in hexanes). ^1H NMR (400 MHz, Methanol- d_4) δ 9.97 (s, 1H), 8.09 (s, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.08 – 6.83 (m, 4H), 6.79 (d, J = 7.9 Hz, 1H), 6.66 (d, J = 9.0 Hz, 1H), 6.38 (d, J = 15.6 Hz, 1H), 5.95 (s, 2H), 3.54 (d, J = 7.5 Hz, 2H), 2.91 (t, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, Methanol- d_4) δ 167.7, 149.9, 149.4, 148.6, 140.2, 129.5, 128.3, 123.9, 123.1, 118.7, 111.5, 111.2, 108.2, 105.9, 102.3, 101.7, 48.1, 47.8, 47.6, 40.3, 25.3. ESI-MS: m/z 351 [M+H]⁺. HRMS (MALDI-TOF) calcd for C₂₀H₁₈N₂O₄Na [M+Na]⁺ 373.1159, found 373.1129.

Synthesis of compound 6

To a solution of compound **3** (296 mg, 0.84 mmol) in DMF (10 mL) was added imidazole (172 mg, 2.53 mmol), TBSCl (152 mg, 1.01 mmol) and stirred at room temperature overnight. Reaction mixture was diluted with EtOAc (50 mL) and washed with saturated aqueous NH₄Cl, H₂O and brine. The organic phase was dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. Crude product was purified using Flash chromatography on Biotage Snap Cartridge (KP-Sil 25 g) using gradient solvent system (30% to 80% ethyl acetate in hexanes) to give product **6** (345 mg, 88% yield). White solid. Mp 68-72 °C. R_f = 0.47 (70% ethyl acetate in hexanes). ^1H NMR (400 MHz, Chloroform- d) δ 7.91 (s, 1H), 7.51 (d, J = 15.5 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.02 (dd, J = 9.4, 2.3 Hz, 2H), 6.98 – 6.91 (m, 2H), 6.78 (dd, J = 8.6, 2.3 Hz, 2H), 6.11 (d, J = 15.5 Hz, 1H), 5.98 (s, 2H), 5.61 (s, 1H), 3.71 (q, J = 6.4 Hz, 2H), 2.98 (t, J = 6.5 Hz,

2H), 0.99 (s, 9H), 0.18 (s, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 166.4, 149.3, 149.2, 148.4, 140.8, 132.3, 129.4, 128.2, 124.1, 123.3, 119.1, 116.5, 111.9, 108.7, 108.4, 106.5, 101.6, 60.7, 40.1, 26.0, 25.5, 18.4, 14.4, -4.2. ESI-MS: m/z 465 $[\text{M}+\text{H}]^+$. HRMS (MALDI-TOF) calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_4\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 487.2024, found 487.2028.

Synthesis of compound 7

To a solution of compound **6** (331 mg, 0.71 mmol) in THF (20 mL) was added DMAP (87 mg, 0.71 mmol), Et_3N (396 μL , 2.82 mmol) and Boc_2O (1.52 g, 6.97 mmol). The reaction mixture was refluxed for 3 hours. Solvent was removed under reduced pressure and the residue was diluted with CH_2Cl_2 (30 mL) and washed with saturated aqueous NH_4Cl , H_2O and brine. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Crude product was purified using Flash chromatography on Biotage Snap Cartridge (KP-Sil 25 g) using gradient solvent system (2% to 40% ethyl acetate in hexanes) to give product **7** (398 mg, 84% yield). White solid. Mp 64-66 °C. R_f = 0.62 (40% ethyl acetate in hexanes). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.95 (s, 1H), 7.63 (d, J = 15.5 Hz, 1H), 7.41 – 7.29 (m, 2H), 7.09 (d, J = 2.1 Hz, 2H), 7.05 (dd, J = 8.0, 1.7 Hz, 1H), 6.87 – 6.77 (m, 2H), 6.00 (s, 2H), 4.07 – 3.95 (m, 2H), 2.92 (t, J = 7.7 Hz, 2H), 1.64 (s, 9H), 1.48 (s, 9H), 1.00 (s, 9H), 0.22 (s, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 168.9, 153.5, 151.6, 149.5, 148.5, 143.3, 129.9, 124.7, 124.1, 119.8, 117.8, 117.8, 115.9, 109.6, 108.7, 106.9, 101.7, 83.3, 45.1, 28.4, 28.3, 26.0, 24.7, 18.5, -4.2. ESI-MS: m/z 565 $[\text{M}+\text{H}-\text{Boc}]^+$. HRMS (MALDI-TOF) calcd for $\text{C}_{36}\text{H}_{48}\text{N}_2\text{O}_8\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 687.3072, found 687.3093.

Synthesis of compound 8

To a solution of compound **7** (301 mg, 0.45 mmol) in THF (10 mL) was added TBAF·3 H_2O (213 mg, 0.68 mmol) and stirred at room temperature for 5 hours. Solvent was removed under reduced pressure and the residue was diluted with EtOAc (30 mL) and washed with H_2O and brine. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Crude product was purified using Flash chromatography on Biotage Snap Cartridge (KP-Sil 25 g) using gradient solvent system (20% to 70% ethyl acetate in hexanes) to give product **8** (232 mg, 93% yield). White solid. Mp 74-78 °C. R_f = 0.48 (40% ethyl acetate in hexanes). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.94 (s, 1H), 7.63 (d, J = 15.5 Hz, 1H), 7.41 – 7.28 (m, 2H), 7.18 (d, J = 2.5 Hz, 1H), 7.07 (d, J = 1.7 Hz, 1H), 7.05 – 6.98 (m, 1H), 6.87 (dd, J = 8.8, 2.5 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.00 (s, 2H), 4.02 – 3.94 (m, 2H), 2.90 (t, J = 7.8 Hz, 2H), 1.63 (s, 9H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 169.3, 153.4, 152.0, 148.5, 143.5, 129.8, 124.8, 124.2, 119.7, 117.5, 116.3, 113.4, 108.8, 106.9, 104.7, 101.7, 83.6, 45.2, 28.4, 28.3, 24.8. ESI-MS: m/z 452 $[\text{M}+\text{H}-\text{Boc}]^+$. HRMS (MALDI-TOF) calcd for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 573.2207, found 573.2204.

Synthesis of compound ($\pm$)-decursivine 1

i) **Without catalyst:** To a solution of compound **8** (30 mg, 0.05 mmol) in HFIP (5 mL) was added PIFA (28 mg, 0.06 mmol) in one portion under Ar atmosphere and stirred at room temperature for 6 hours. To this was then added TFA (20 μ L, 0.26 mmol) and the reaction mixture was stirred at room temperature overnight. Reaction was quenched with saturated aqueous NaHCO₃ and extracted with EtOAC (3 $\times$ 20 mL). Combined organic phase was dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. Crude product was purified using Flash chromatography on Biotage Snap Cartridge (KP-Sil 10 g) using gradient solvent system (30% to 90% ethyl acetate in hexanes) to give product **1** (9 mg, 47% yield) as beige solid. Mp $\approx$ 250 $^{\circ}$ C, literature⁴ Mp 260 $^{\circ}$ C (dec.). R_f = 0.15 (50% ethyl acetate in hexanes). ¹H NMR (400 MHz, Pyridine-*d*₅) ^{1,5,6,8} δ 12.08 (s, 1H), 8.87 (dd, J = 10.3, 4.8 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.39 (s, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.08 (t, J = 8.9 Hz, 2H), 6.94 (d, J = 7.9 Hz, 1H), 5.98 (s, 2H), 4.24 – 4.10 (m, 1H), 3.59 (dd, J = 15.8, 3.9 Hz, 1H), 3.22 – 3.16 (m, 2H). ESI-MS: m/z 349 [M+H]⁺. HRMS (MALDI-TOF) calcd for C₂₀H₁₆N₂O₄Na [M+Na]⁺ 1002, found 371.1006.

ii) **With catalyst:** To a solution of compound **8** (30 mg, 0.05 mmol) in HFIP (5 mL) was added ($\pm$)-BINOL phosphoric acid (1 mg, 0.0025 mmol) and PIFA (28 mg, 0.06 mmol) in one portion under Ar atmosphere. The reaction mixture was stirred at room temperature for 3 hours. To this was then added TFA (20 μ L, 0.26 mmol) and the reaction mixture was stirred at room temperature overnight. Reaction was quenched with saturated aqueous NaHCO₃ and extracted with EtOAC (3 $\times$ 20 mL). Combined organic phase was dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. Crude product was purified using Flash chromatography on Biotage Snap Cartridge (KP-Sil 10 g) using gradient solvent system (30% to 90% ethyl acetate in hexanes) to give product **1** (14 mg, 74% yield). ¹H NMR and mass data are same as mentioned above and matches with the literature data.^{1,5,6,8}

Declarations

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Author Contributions

P.T.P. and R.M. designed the experiments. P.T.P. performed all the experiments and analyzed the data. P.T.P. and R.M. wrote the manuscript. E.S.S. helped in performing electrochemistry experiments. All authors have given approval to the final version of the manuscript.

Competing Interests

The authors declare no competing interests.

Additional Information

Copies of ^1H and ^{13}C NMR of all new compounds available in the supporting information.

References

- 1 Zhang, H. J. *et al.* Antimalarial agents from plants - II. Decursivine, a new antimalarial indole alkaloid from *Rhaphidophora decursiva*. *Pharm Biol* **40**, 221-224 (2002).
- 2 Sato, H. *et al.* Serotobenine, a Novel Phenolic Amide from Safflower Seeds (*Carthamus-Tinctorius* L). *Agr Biol Chem Tokyo* **49**, 2969-2974 (1985).
- 3 Chen, Z., Pitchakuntla, M. & Jia, Y. X. Synthetic approaches to natural products containing 2,3-dihydrobenzofuran skeleton. *Nat Prod Rep* **36**, 666-690 (2019).
- 4 Leduc, A. B. & Kerr, M. A. Total synthesis of (+/-)-decursivine. *Eur J Org Chem* **2007**, 237-240 (2007).
- 5 Qin, H., Xu, Z. R., Cui, Y. X. & Jia, Y. X. Total Synthesis of (+/-)-Decursivine and (+/-)-Serotobenine: A Witkop Photocyclization/Elimination/O-Michael Addition Cascade Approach. *Angew Chem Int Edit* **50**, 4447-4449 (2011).
- 6 Mascal, M., Modes, K. V. & Durmus, A. Concise Photochemical Synthesis of the Antimalarial Indole Alkaloid Decursivine. *Angew Chem Int Edit* **50**, 4445-4446 (2011).
- 7 Hu, W. M., Qin, H., Cui, Y. X. & Jia, Y. X. Total Synthesis of (+)- and (-)-Decursivine and (+/-)-Serotobenine through a Cascade Witkop Photocyclization/Elimination/Addition Sequence: Scope and Mechanistic Insights. *Chem-Eur J* **19**, 3139-3147 (2013).
- 8 Sun, D. Q., Zhao, Q. W. & Li, C. Z. Total Synthesis of (+)-Decursivine. *Org Lett* **13**, 5302-5305 (2011).
- 9 Guo, L., Zhang, F. Y., Hu, W. M., Li, L. & Jia, Y. X. Palladium-catalyzed synthesis of benzofurans via C-H activation/oxidation tandem reaction and its application to the synthesis of decursivine and serotobenine. *Chem Commun* **50**, 3299-3302 (2014).
- 10 Zhang, F. Y., Guo, L., Hu, W. M. & Jia, Y. X. Total synthesis of (-)-decursivine and analogues via cascade sequence. *Tetrahedron* **71**, 3756-3762 (2015).
- 11 Liang, K. J. *et al.* Biomimetic Synthesis of Moschamine-Related Indole Alkaloids via Iron-Catalyzed Selectively Oxidative Radical Coupling. *Org Lett* **18**, 1474-1477 (2016).
- 12 Neelarapu, R. *et al.* Design and Synthesis of Orally Bioavailable Piperazine Substituted 4(1H)-Quinolones with Potent Antimalarial Activity: Structure-Activity and Structure-Property Relationship Studies. *J Med Chem* **61**, 1450-1473 (2018).

- 13 Maignan, J. R. *et al.* ICI 56,780 Optimization: Structure-Activity Relationship Studies of 7-(2-Phenoxyethoxy)-4(1H)-quinolones with Antimalarial Activity. *J Med Chem* **59**, 6943-6960 (2016).
- 14 Cross, R. M. *et al.* Orally Bioavailable 6-Chloro-7-methoxy-4(1H)-quinolones Efficacious against Multiple Stages of Plasmodium. *J Med Chem* **57**, 8860-8879 (2014).
- 15 Monastyrskiy, A., Kyle, D. E. & Manetsch, R. 4(1H)-Pyridone and 4(1H)-Quinolone Derivatives as Antimalarials with Erythrocytic, Exoerythrocytic, and Transmission Blocking Activities. *Curr Top Med Chem* **14**, 1693-1705 (2014).
- 16 Parvatkar, P. T., Parameswaran, P. S. & Tilve, S. G. An Expedient I-2-Catalyzed Entry into 6H-Indolo[2,3-b]quinoline System of Cryptotackieine. *J Org Chem* **74**, 8369-8372 (2009).
- 17 Parvatkar, P. T., Ajay, A. K., Bhat, M. K., Parameswaran, P. S. & Tilve, S. G. Iodine catalyzed one-pot synthesis of chloro-substituted linear and angular indoloquinolines and in vitro antiproliferative activity study of different indoloquinolines. *Med Chem Res* **22**, 88-93 (2013).
- 18 Parvatkar, P. T. & Majik, M. S. Microwave-assisted reductive cyclization: an easy entry to the indoloquinolines and spiro[2H-indole-2,3'-oxindole]. *Rsc Adv* **4**, 22481-22486 (2014).
- 19 Parvatkar, P. T. & Hive, S. G. An efficient synthesis of indoloquinoline alkaloid-neocryptolepine (cryptotackieine). *Tetrahedron Lett* **52**, 6594-6596 (2011).
- 20 Wang, S. P., Gates, B. D. & Swenton, J. S. A Convergent Route to Dihydrobenzofuran Neolignans Via a Formal 1,3-Cycloaddition to Oxidized Phenols. *J Org Chem* **56**, 1979-1981 (1991).
- 21 Berard, D., Jean, A. & Canesi, S. Novel formal [2+3] cycloaddition between substituted phenols and furan. *Tetrahedron Lett* **48**, 8238-8241 (2007).
- 22 Berard, D., Racicot, L., Sabot, C. & Canesi, S. Formal [2+3] cycloaddition between substituted phenols and allylsilane. *Synlett*, 1076-1080 (2008).
- 23 Berard, D., Giroux, M. A., Racicot, L., Sabot, C. & Canesi, S. Intriguing formal [2+3] cycloaddition promoted by a hypervalent iodine reagent. *Tetrahedron* **64**, 7537-7544 (2008).
- 24 Mohr, A. L., Lombardo, V. M., Arisco, T. M. & Morrow, G. W. Synthesis of Pterocarpin-Type Heterocycles via Oxidative Cycloadditions of Phenols and Electron-Rich Arenes. *Synthetic Commun* **39**, 3845-3855 (2009).
- 25 Gelis, C., Bekkaye, M., Lebee, C., Blanchard, F. & Masson, G. Chiral Phosphoric Acid Catalyzed [3+2] Cycloaddition and Tandem Oxidative [3+2] Cycloaddition: Asymmetric Synthesis of Substituted 3-Aminodihydrobenzofurans. *Org Lett* **18**, 3422-3425 (2016).

Figures

Figure 1

Chemical structures of naturally occurring (+)-decursivine 1 and (±)-serotobenine 2.

Figure 2

Retrosynthetic pathway of (±)-decursivine 1

Figure 3

Attempted synthesis of (±)-decursivine 1

Figure 4

Total synthesis of (±)-decursivine 1

Figure 5

Probable mechanism of tandem oxidative cyclization

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