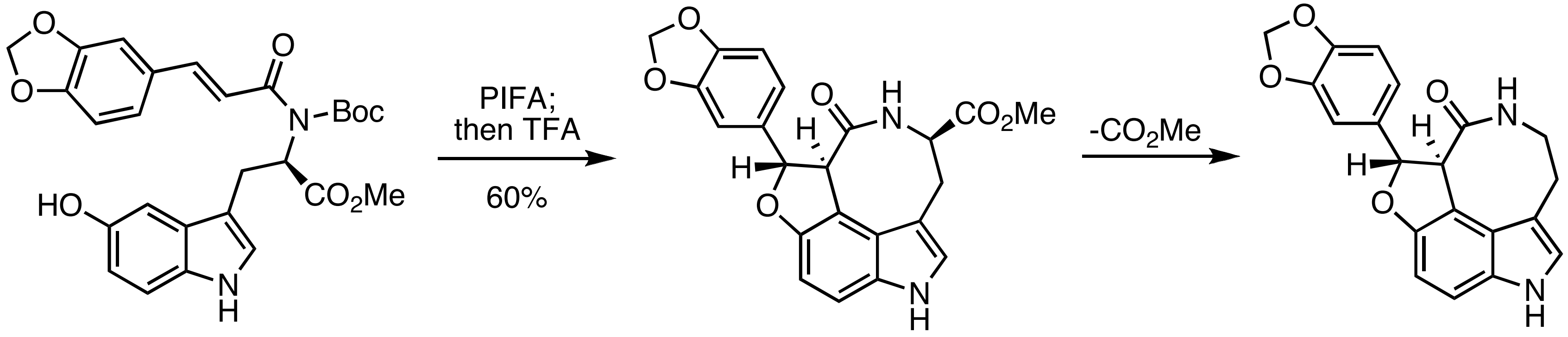
Total Synthesis of (+)-Decursivine

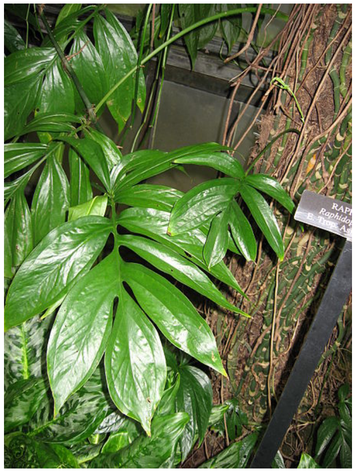
Sun, D.; Zhao, Q.; Li, C. *Org. Lett.* **2011**, *ASAP.*
DOI: 10.1021/ol2021669

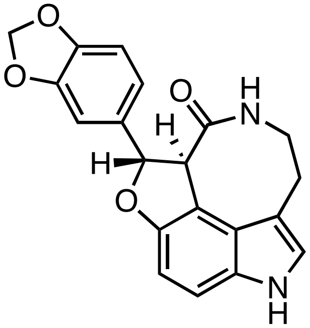


(+)-decursivine

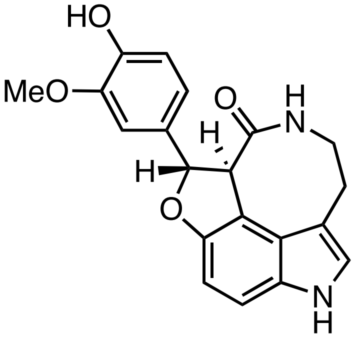
Kara George Rosenker
Wipf Group Current Literature
8 October 2011

(+)-Decursivine: Isolation and Biological Activity





(+)-decursivine

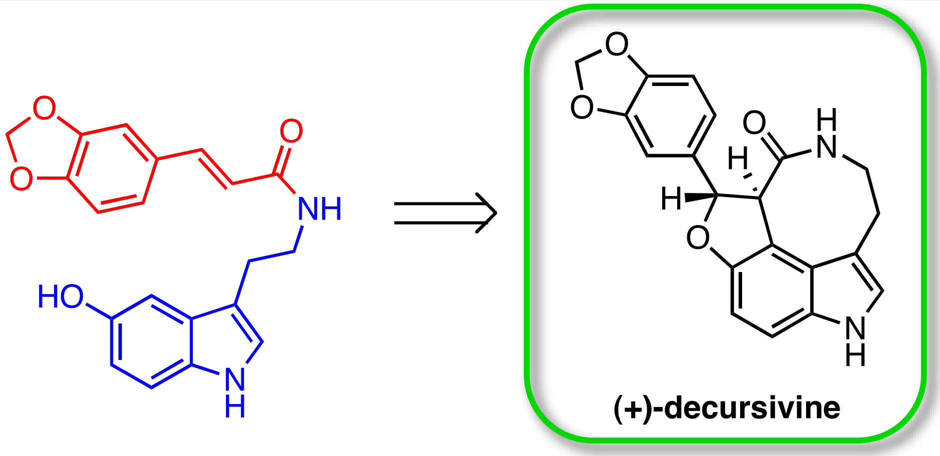


(±)-serotobenine

- (+)-Decursivine was isolated in 2002 from the leaves and stems of *Rhaphidophora decursiva*, a perenial, evergreen vine found in the Cuc Phuong National Park in Vietnam
- (+)-Decursivine exhibits moderate antimalarial activity against the chloroquinine-resistant *Plasmodium falciparum* (IC_{50} = 4.4 μg/mL)
- Structurally similar (±)-serotobenine was also isolated from the leaf extract; however, it showed no activity against *Plasmodium falciparum*
- Synthetic challenges include the sensitivity of the electron-rich indole to oxidation, the construction of the stereogenic centers on the dihydrobenzofuran, and the formation of the eight-membered lactam

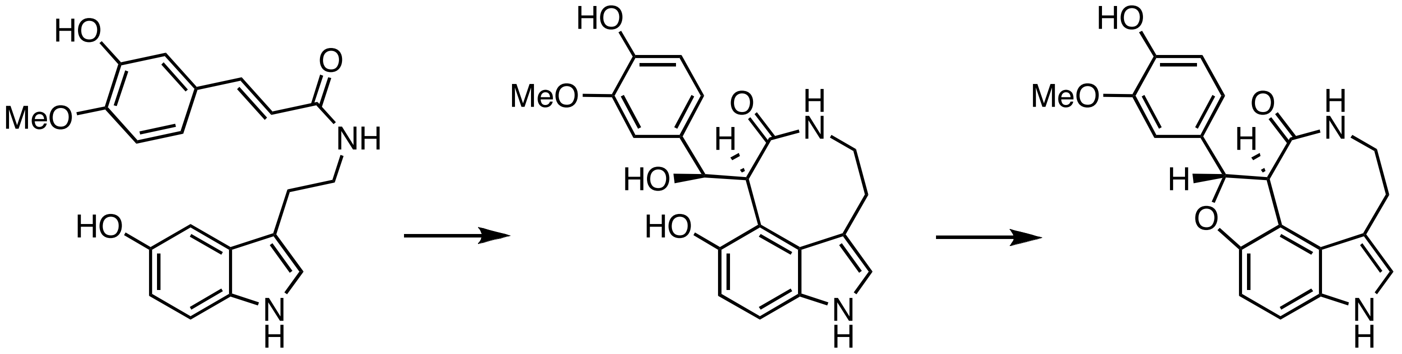
Zhang, H.; Qiu, S.; Tamez, P.; Tan, G. T.; Aydogmus, Z.; Hung, N. V.; Cuong, N. M.; Angerhofer, C.; Soejarto, D. D.; Pezzuto, J. M.; Fong, H. H. S. *Pharm. Biol.* **2002**, *40*, 221-224.
Leduc, A. B.; Kerr, M. A. *Eur. J. Org. Chem.* **2007**, 237-240.
Mascal, M.; Modes, K. V.; Durmus, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 4445-4446.
Qin, H.; Xu, Z.; Cui, Y.; Jia, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 4447-4449.

Biosynthesis of (±)-Serotobenine & (+)-Decursivine



(+)-decursivine

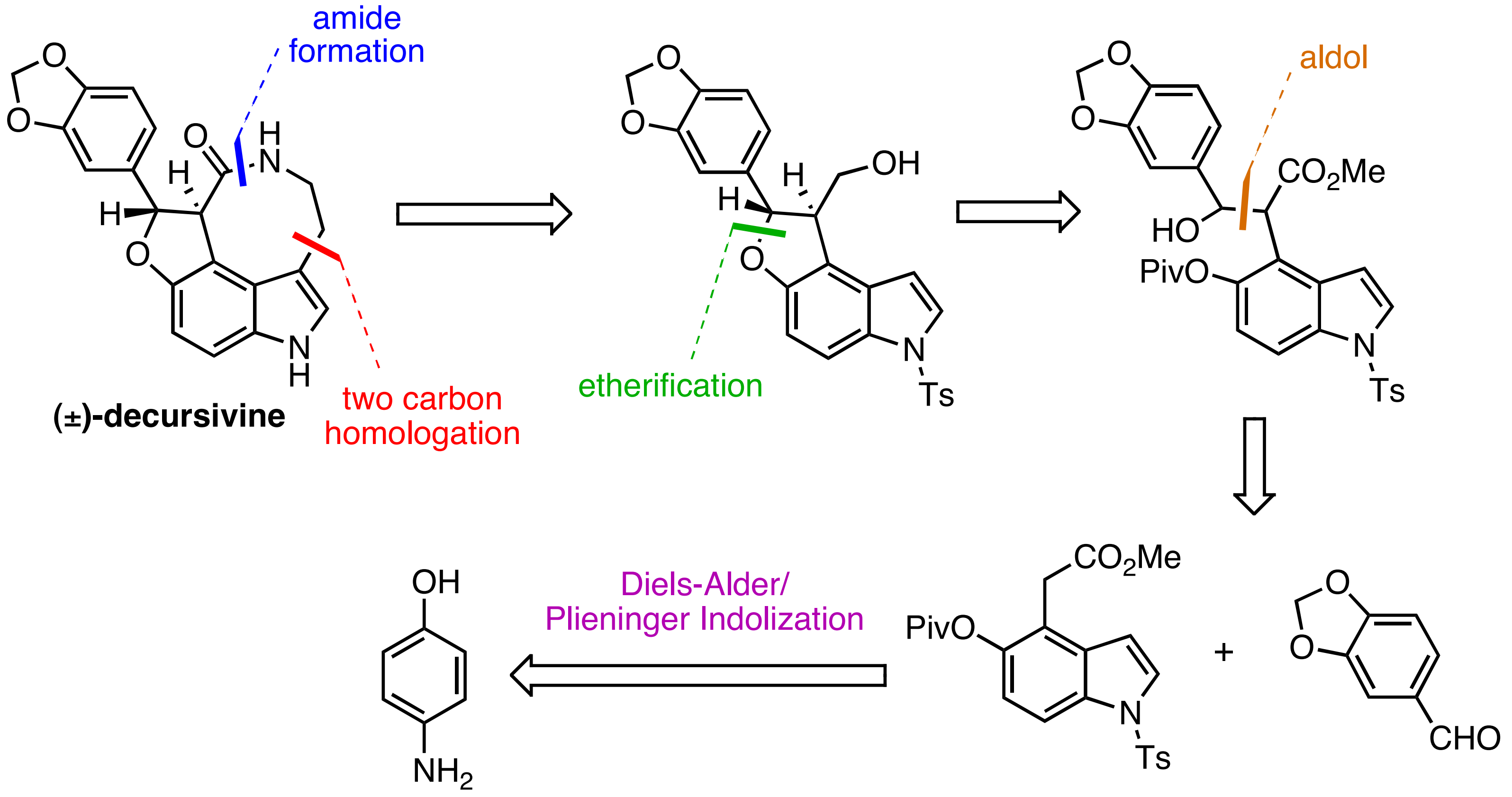
- The biosynthesis of both (+)-decursivine and (±)-serotobenine likely involves the cyclization of a cinnamide composed of serotonin and an appropriately substituted cinnamic acid
- This is supported by the co-isolation of moschamine, moschaminindolol, and serotobenine



moschamine **moschaminindolol** **(±)-serotobenine**

Sato, H.; Kawagishi, H; Nishimura, T.; Yoneyama, S.; Yoshimoto, Y.; Sakamura, S.; Furusaki, A.; Katsuragi, S.; Matsumoto, T. *Agric. Biol. Chem.* **1985**, *49*, 2969-2974.
Sakamura, S.; Terayama, Y.; Kawakatsu, S.; Ichihara, A.; Saito, H. *Agric. Biol. Chem.* **1978**, *42*, 1805-1806.
Sakamura, S.; Terayama, Y.; Kawakatsu, S.; Ichihara, A.; Saito, H. *Agric. Biol. Chem.* **1980**, *44*, 2951-2954.

First Total Synthesis of (±)-Decursivine

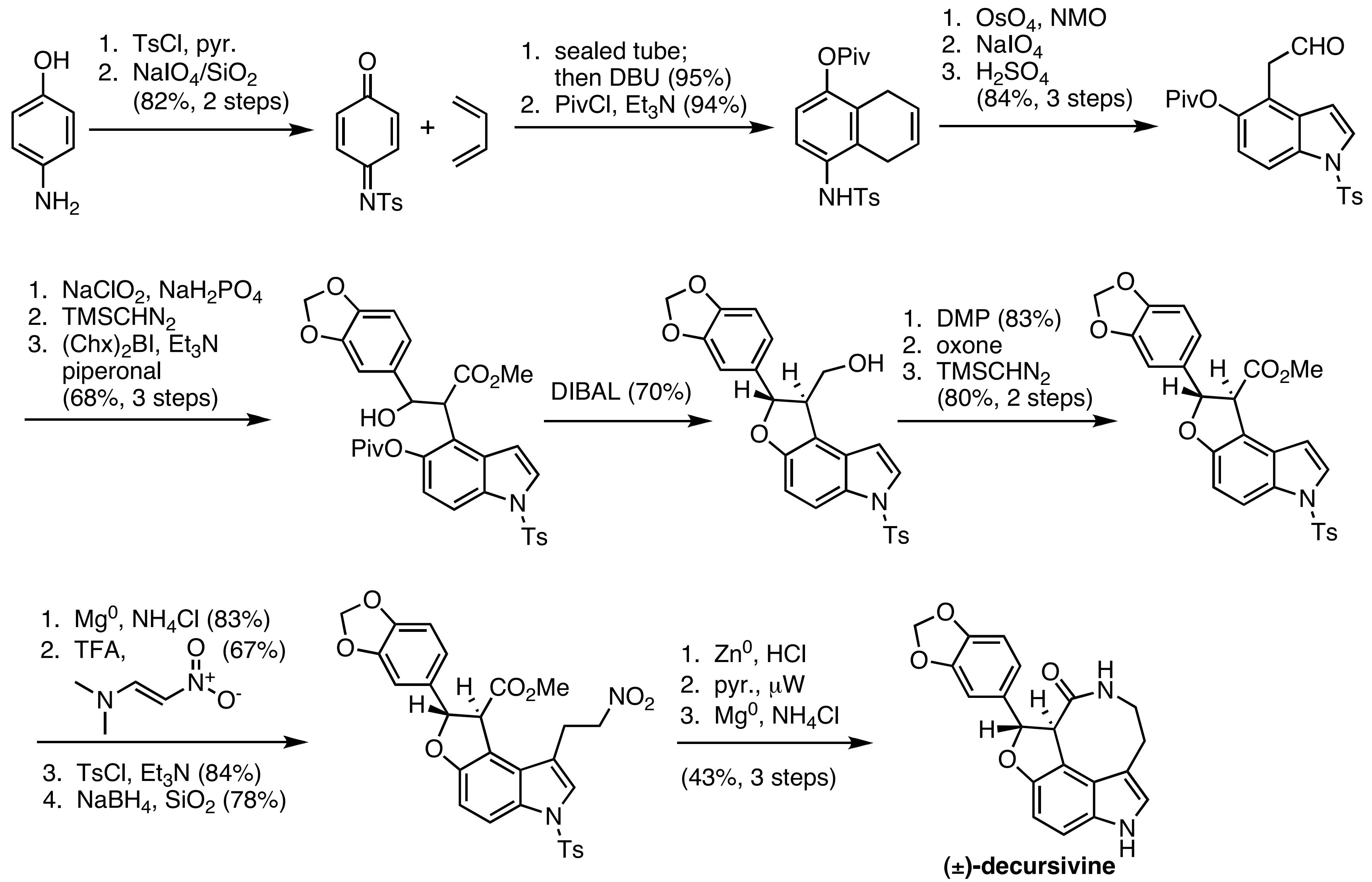


Reported by Kerr and co-workers in 2007

Key Feature: Diels-Alder/Plieninger indolization

Leduc, A. B.; Kerr, M. A. *Eur. J. Org. Chem.* **2007**, 237-240.

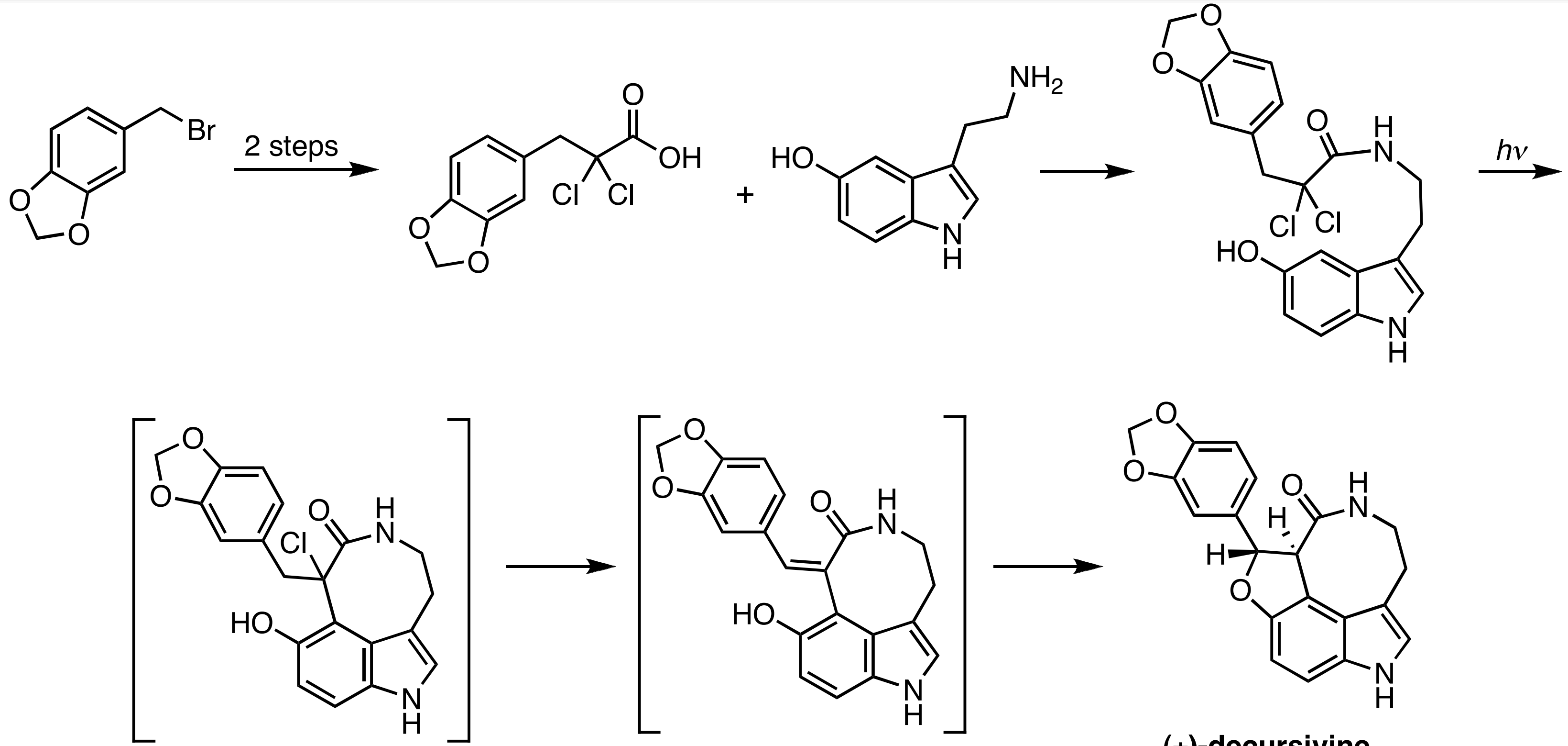
First Total Synthesis of (±)-Decursivine



20 Steps, 2.5% overall yield

Leduc, A. B.; Kerr, M. A. *Eur. J. Org. Chem.* **2007**, 237-240.

Expedient Syntheses of (±)-Decursivine



(±)-decursivine

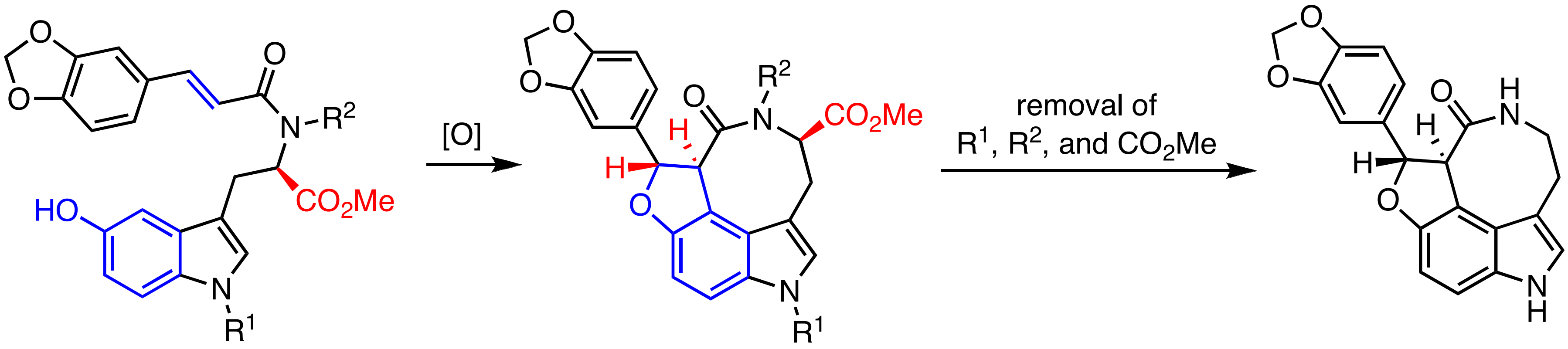
Key Step: Witkop photocylcization/elimination/*O*-Michael addition

Mascal and co-workers: 4 steps, 53% overall yield

Jia and co-workers: 4 steps, 20% overall yield

Mascal, M.; Modes, K. V.; Durmus, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 4445-4446.
Qin, H.; Xu, Z.; Cui, Y.; Jia, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 4447-4449.

Title Paper: Synthetic Design of (+)-Decursivine



(+)-decursivine

Strategy includes:

- Biomimetic stereoselective oxidative intramolecular [3+2] cycloaddition
- Chirality transfer from the tryptophan to the two newly formed chiral centers

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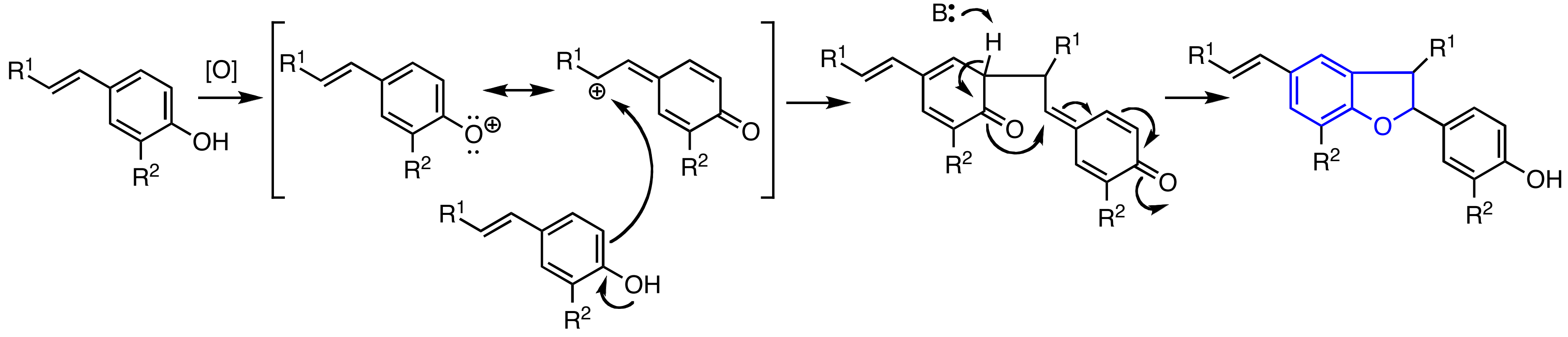
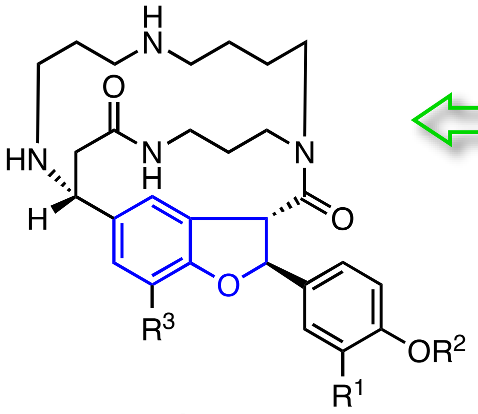
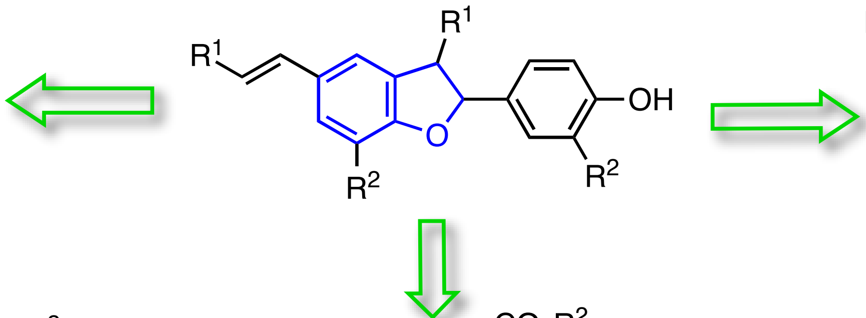
Oxidative Dimerization of Substituted *P*-Hydroxystyrenes

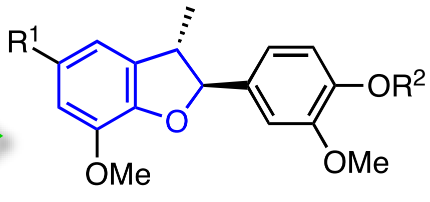


[O]: $PhI(OAc)_2$, Ag_2O, $K_3[Fe(CN)_6]$, or HRP/H_2O_2

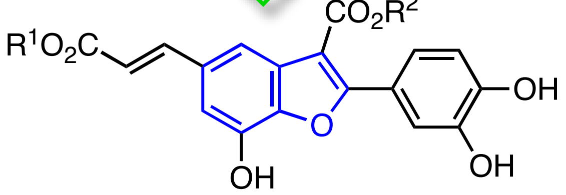


ephedradine A-D &
***O*-methylorantine**





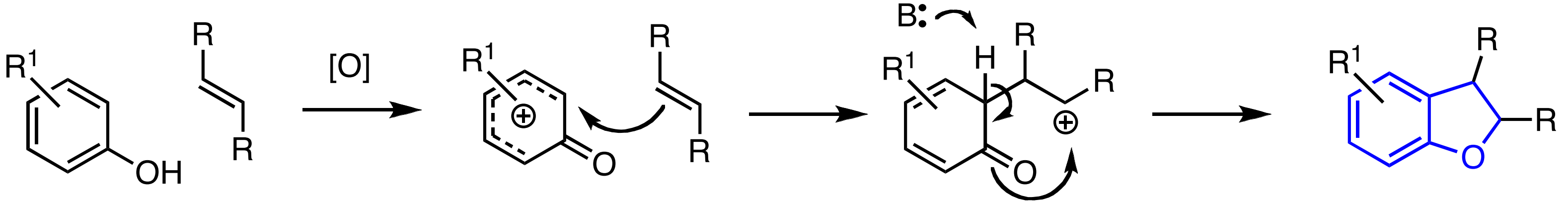
fragnasols A-C &
dehydrodiisoeugenol



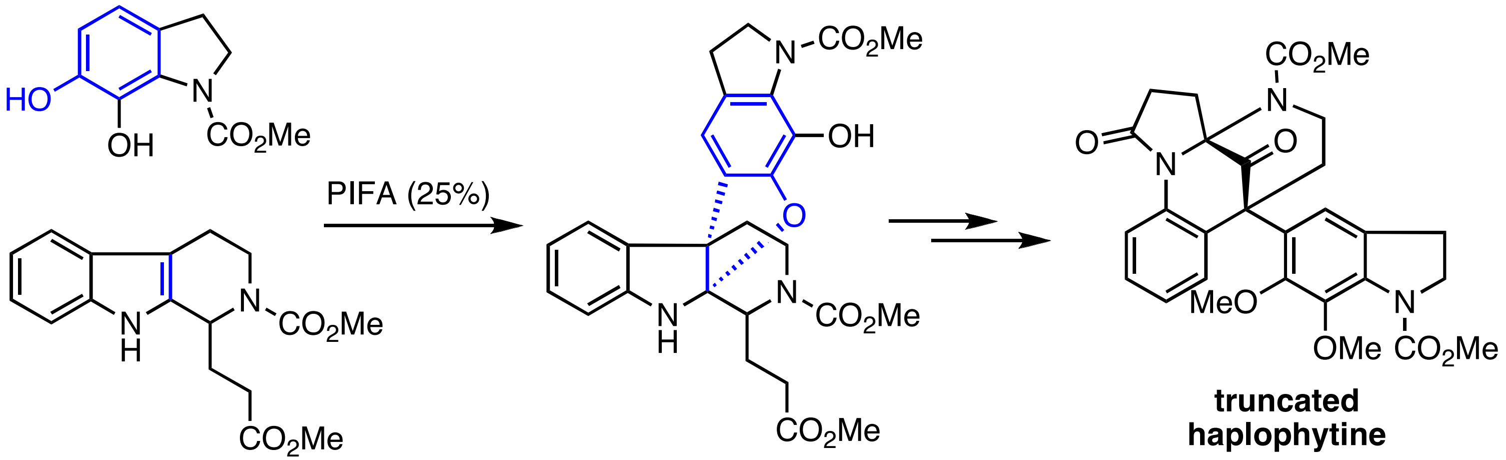
schizotenuins 1-3

Juhász, L.; Kürti, L.; Antus, S. *J. Nat. Prod.* **2000**, *63*, 866-870.
Maeda, S.; Masuda, H.; Tokoroyama, T. *Chem. Pharm. Bull.* **1994**, *42*, 2500-2505.
Wasserman, H. H.; Brunner, R. K.; Buynak, J. D.; Carter, C. G.; Oku, T.; Robinson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 519-521.

Oxidative [3+2] Cycloaddition: Phenols and Electron-Rich Alkenes



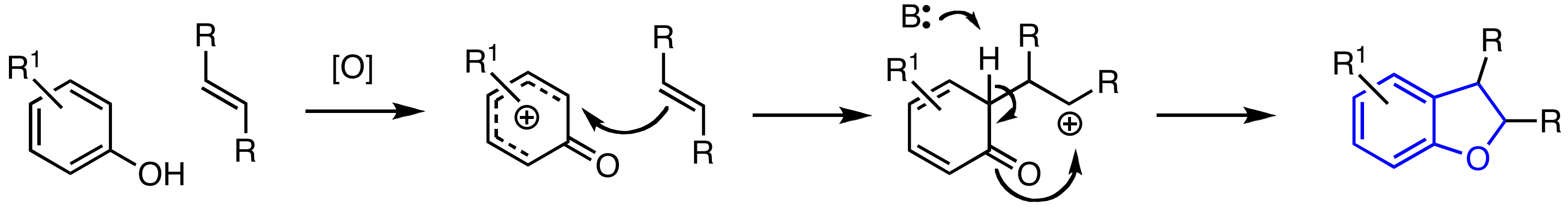
[O]: PIFA, PhI(OAc)$_2$, or HRP/H$_2$O$_2$



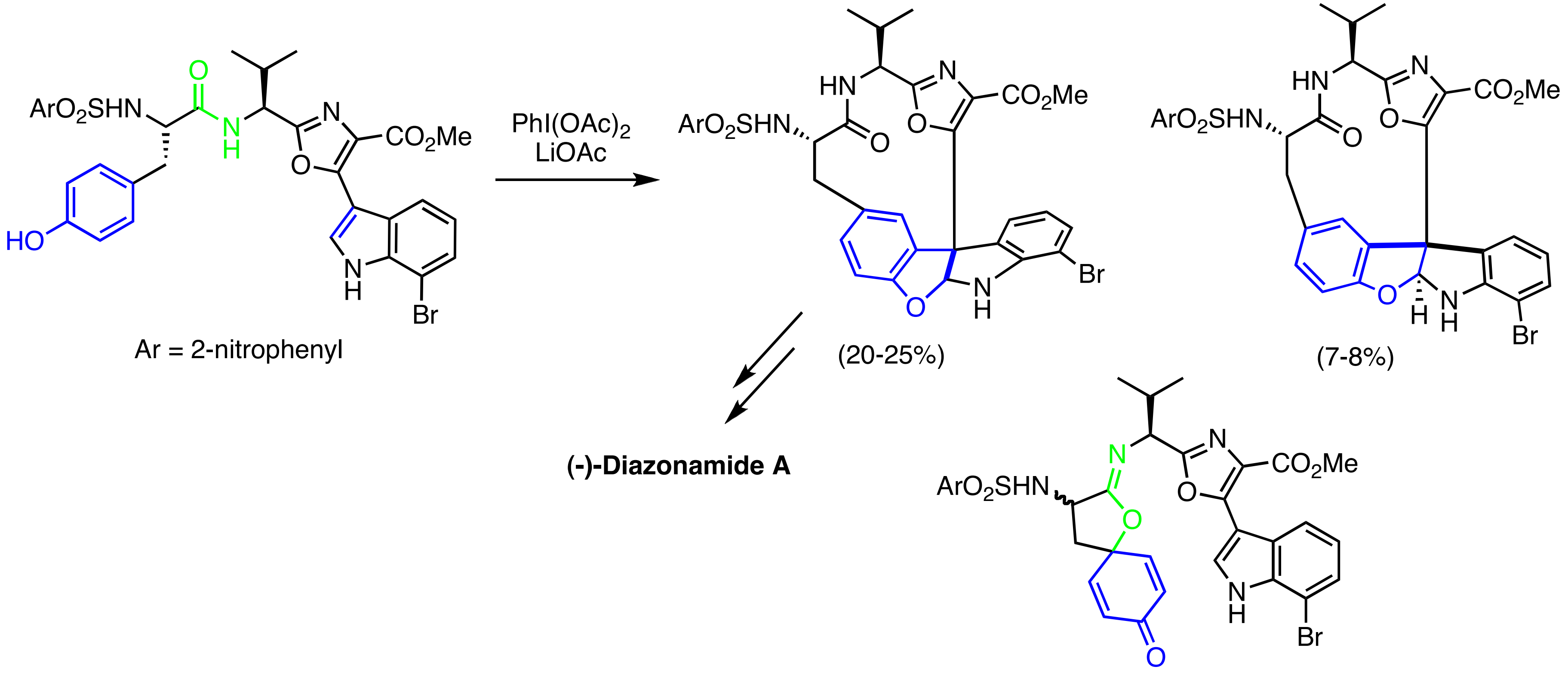
truncated haplophytine

Nicolaou, K. C.; Majumder, U.; Roche, S. P.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4715-4718.

Intramolecular Oxidative [3+2] Cycloaddition: Diazonamide A



[O]: PIFA, $PhI(OAc)_2$, or HRP/H_2O_2



Ar = 2-nitrophenyl

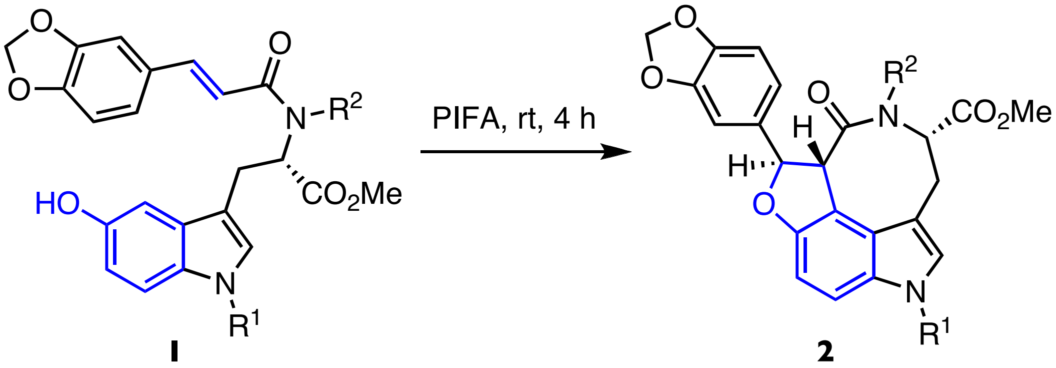
(20-25%)

(7-8%)

(15%, 1:1)

Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4961-4966.

Title Paper: Optimization of the [3+2] Cycloaddition



entry[a]	I	R1	R2	solvent	2	yield (%)[b]
1	1a	H	H	TFE	2a	0
2	1b	CO_2Bn	H	TFE	2b	0
3	1c	H	Bn	TFE	2c	0
4	1d	Bn	Bn	TFE	2d	0
5	1e	Ts	Bn	TFE	2e	20
6	1f	CO_2Bn	Bn	TFE	2f	24
7	1f	CO_2Bn	Bn	HFIP	2f	41
8[c]	1f	CO_2Bn	Bn	HFIP	2f	66

[a] Reaction conditions: **I** (0.05 mmol), PIFA (0.06 mmol), TFE or HFIP (1 mL), rt, 4 h. [b] Isolated yield based on **I**. [c] 5 mL of HFIP were used.

- Changing the oxidant to $PhI(OAc)_2$ led to a decrease in product yield.
- Increased and decreased reaction temperatures did not improve the product yield.

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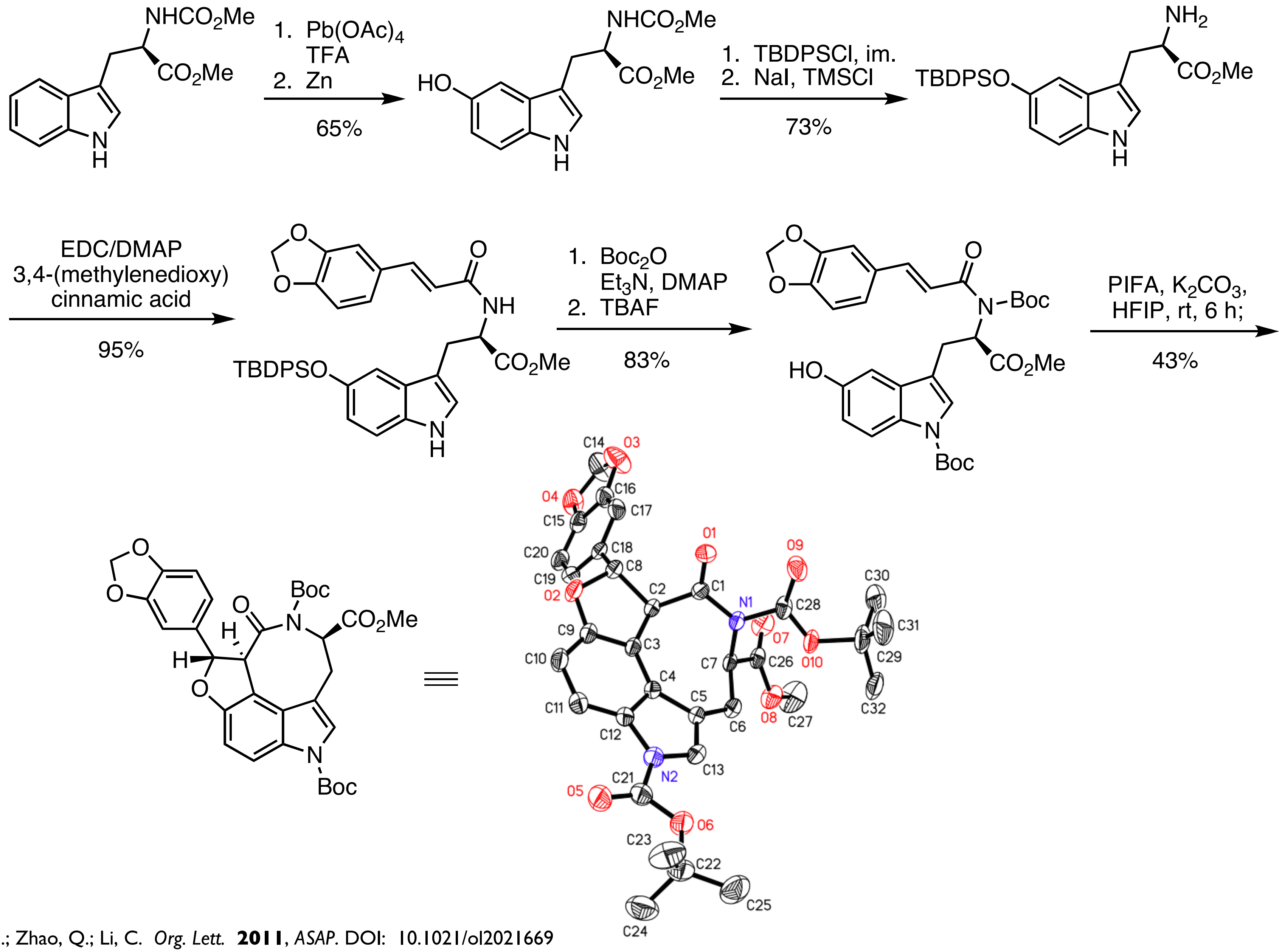

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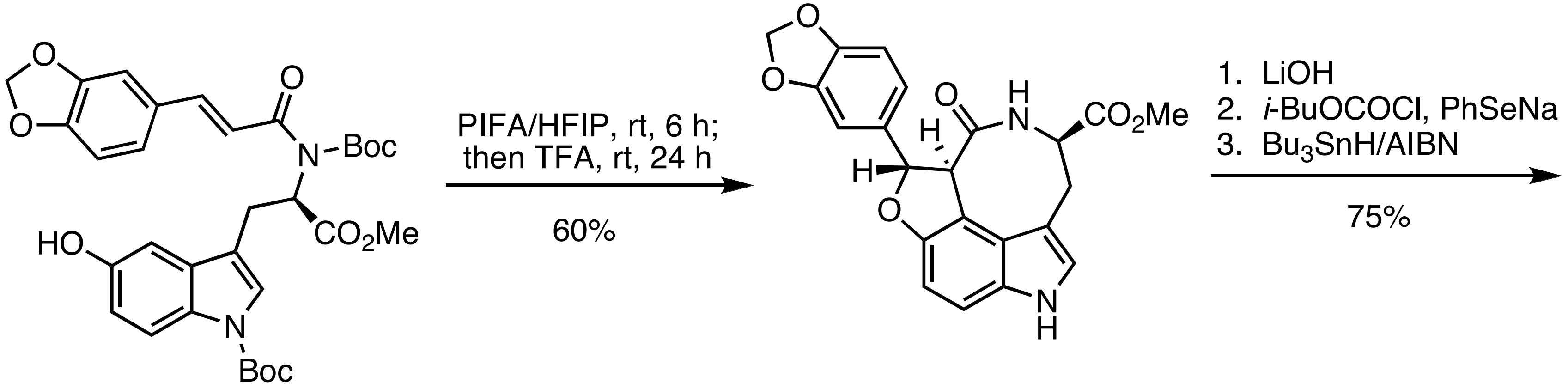
Total Synthesis of (+)-Decursivine

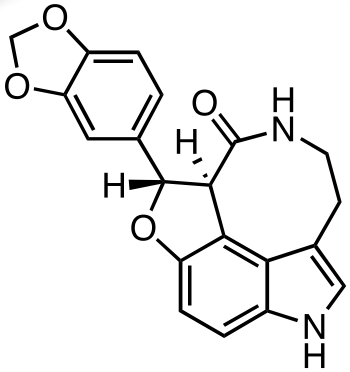


PIFA/HFIP, rt, 6 h; then TFA, rt, 24 h

60%

1. LiOH
2. *i*-BuOCOCl, PhSeNa
3. $Bu_3SnH/AIBN$

75%



(+)-decursivine

10 steps, 16.7% overall yield

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Conclusion

- Li and co-workers accomplished the first asymmetric synthesis of (+)-decursivine in 10 steps and a 16.7% overall yield
- Key features of their synthesis include:
  - PIFA-mediated oxidative intramolecular [3+2] cycloaddition of 5-hydroxytryptophans with substituted cinnamamides in a highly diasteroselective manner
  - Traceless chirality transfer from the starting tryptophan to the target molecule
- Application of this oxidative intramolecular [3+2] cycloaddition provides an additional methodology for accessing dihydrobenzofurans

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