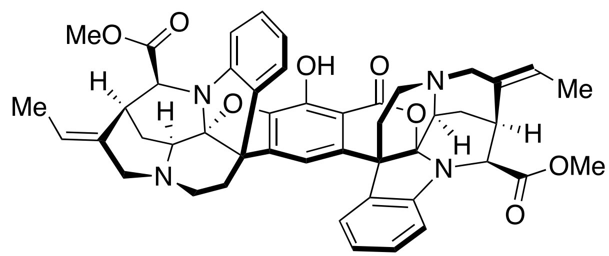
Unified biomimetic assembly of voacalgine A and bipleiophylline via divergent oxidative couplings



Lachkar, D.; Denizot, N.; Beradat, G.; Ahamada, K.; Beniddir, M.A.; Dumontet, V.; Gallard, J.F.; Guillot, R.; Leblanc, K.; N'nang, E.O.; Turpin, V.; Kouklovsky, C.; Poupon, E.; Evanno, L.; Vincent, G.

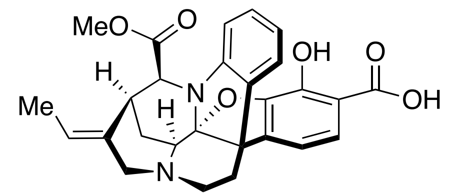
Nat. Chem. **2017**, *AOP.*

Tim McFadden, Current Literature, 5/6/17

Introduction – Natural Products

Voacolgine A

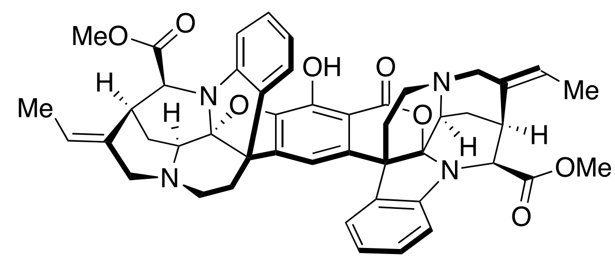
-monoindole alkaloid
-isolated from *voacanga grandifolia*
-possible biosynthetic precursor to bipleiophylline
-has shown moderate cell growth inhibitory effects against HL-60 and HCT116 cells



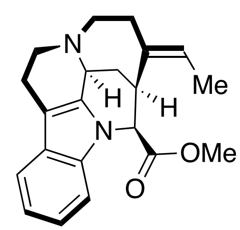
voacalgine A (originally assigned structure)

Bipleiophylline

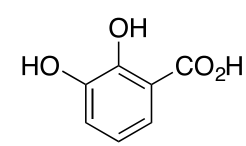
-bisindole alkaloid with "aromatic spacer"
-isolated from *Alstonia angustifolia*
-biological activity not reported
-synthetic "mountain to climb" due to complexity



bipleiophylline



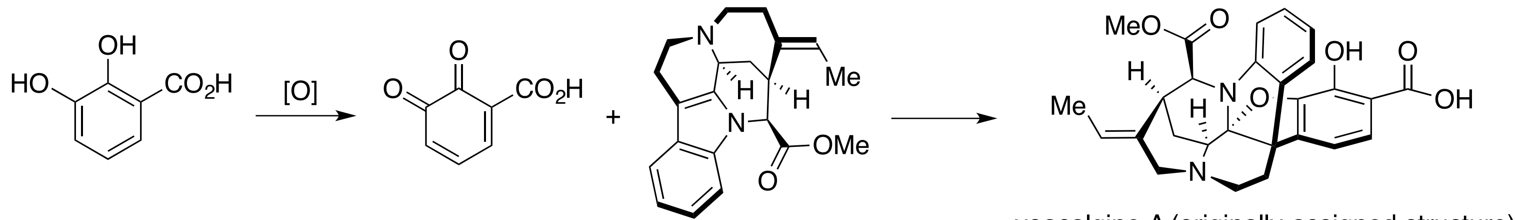
pleiocarpamine



pyrocatechuic acid

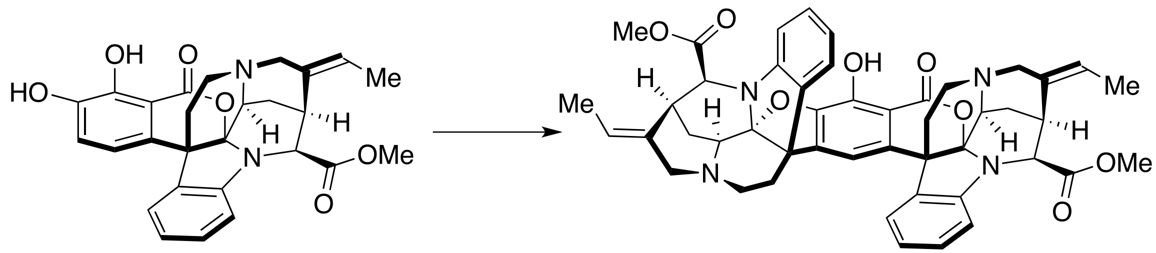
Tetrahedron, **2013**, *69*, 10869–75.
Org. Lett. **2008**, *10*, 3749–52.
Design and Strategy in Organic Synthesis: From the Chiron Approach to Catalysis (Wiley-VCH, 2013).

Introduction – Biosynthesis, Strategy



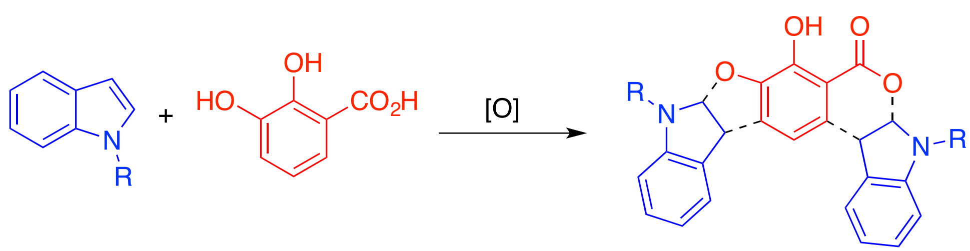
pleiocarpamine

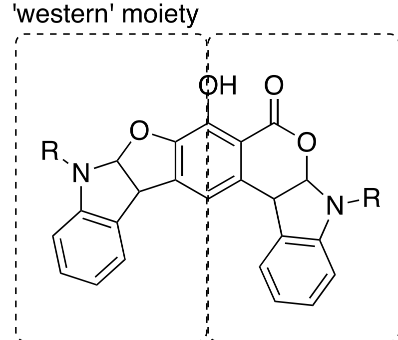
voacalgine A (originally assigned structure)
biosynthetic dead-end?



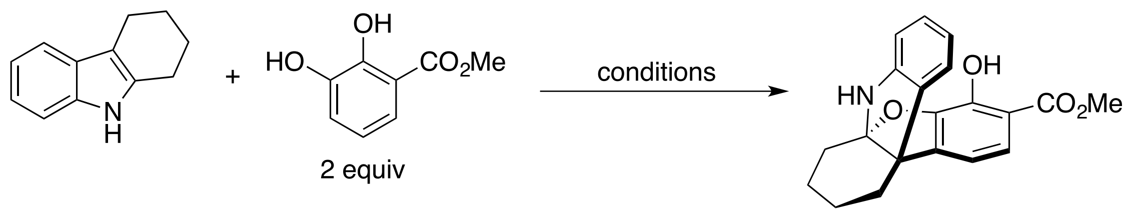
voacalgine A (revised structure)

bipleiophylline



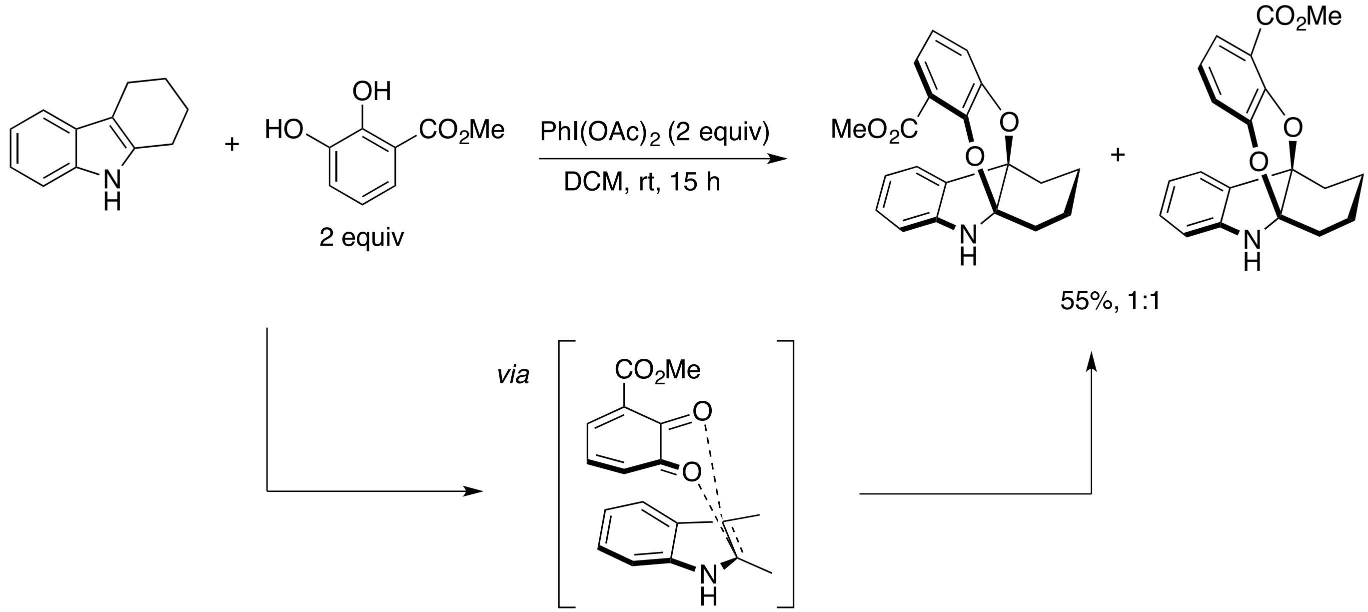


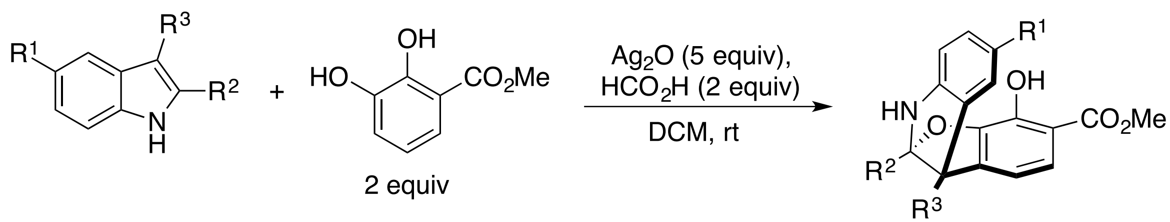
Western Moiety: Reaction Optimization

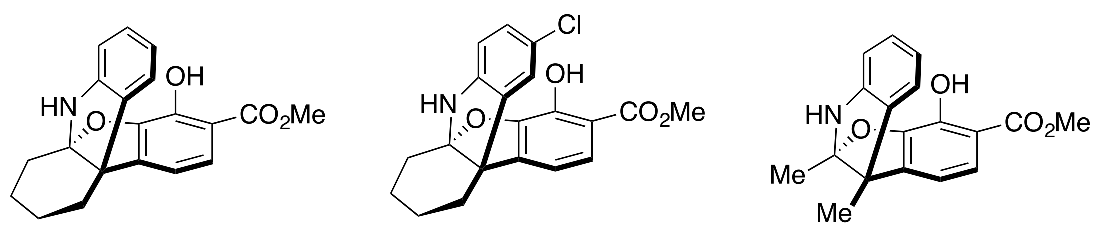


entry	oxidant	solvent	additive	time	isolated yield
1	$K_3[Fe(CN)_6]$	-	-	-	0%
2	DDQ	-	-	-	0%
3	CAN	-	-	-	0%
4	$NaIO_4$	-	-	-	0%
5	$PhI(OAc)_2$	DCM	none	15 h	0%, but…
6	Ag_2O	DCM	none	6 h	14%
7	Ag_2O	MeCN	none	6 h	trace
8	**Ag_2O**	**DCM**	**HCO_2H (2 equiv)**	**40 min**	**38%**

Western Moiety, Diels-Alder Side Reaction



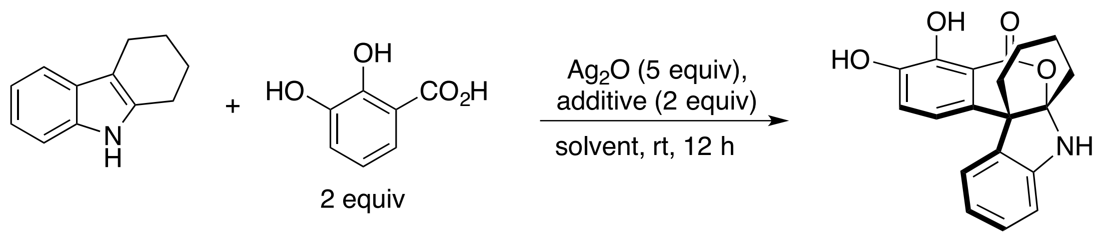




38%, 40 min | 18%, 90 min | 19%, 90 min

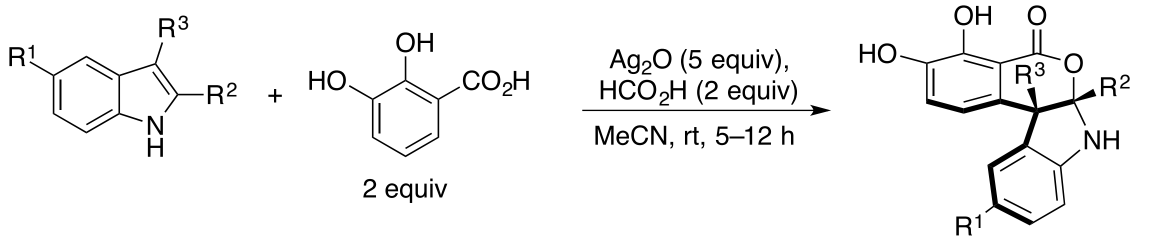
5

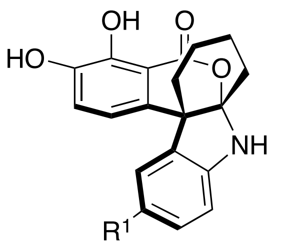
Eastern Moiety: Optimization



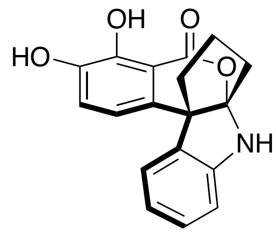
entry	solvent	additive	isolated yield
1	DCM	none	10%
2	MeCN	none	51%
3	**MeCN**	**HCO_2H**	**63%**
4	HCO_2H	none	0% (decomp)

Eastern Moiety: Scope

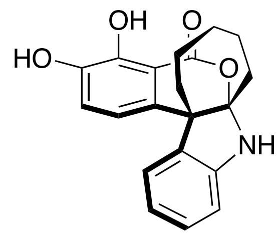




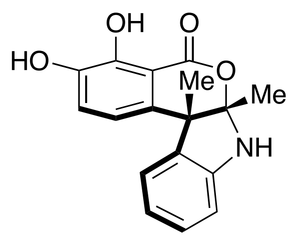
R^1=H, 62%
R^1=MeO, 45%
R^1=Me, 64%
R^1=F, 64%
R^1=Cl, 71%
R^1=Br, 62%



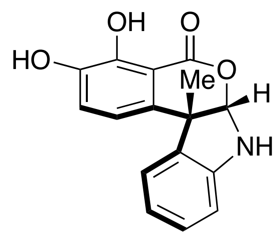
67%



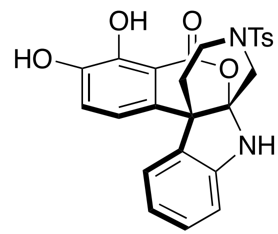
31%



53%

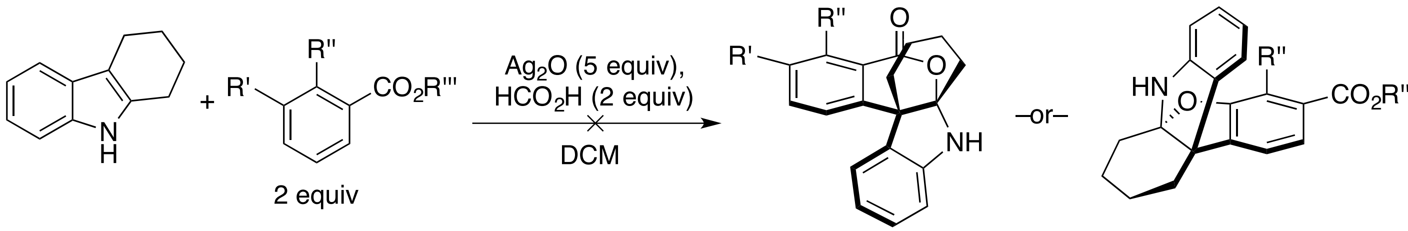


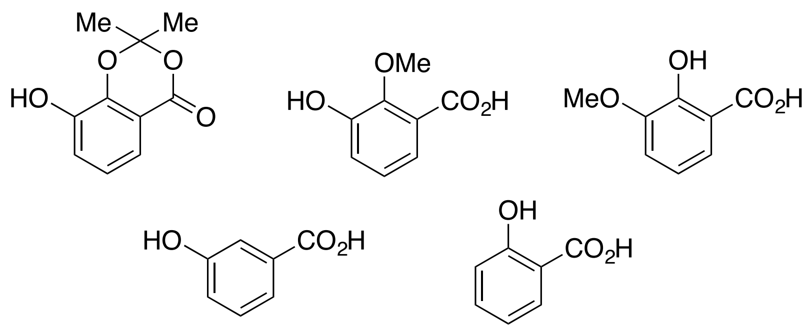
62%



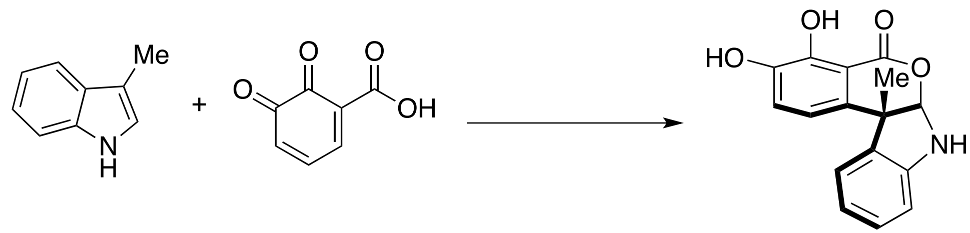
30%

Mechanism – Control Reactions

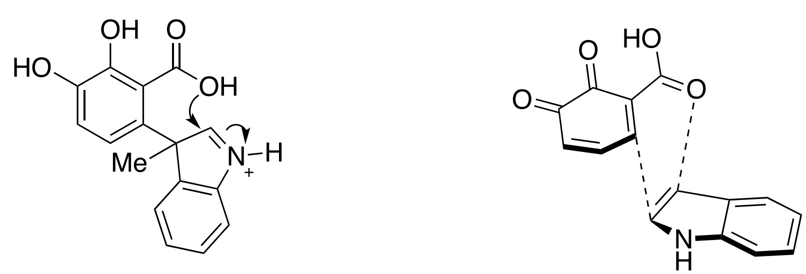




Mechanism – Calculations I

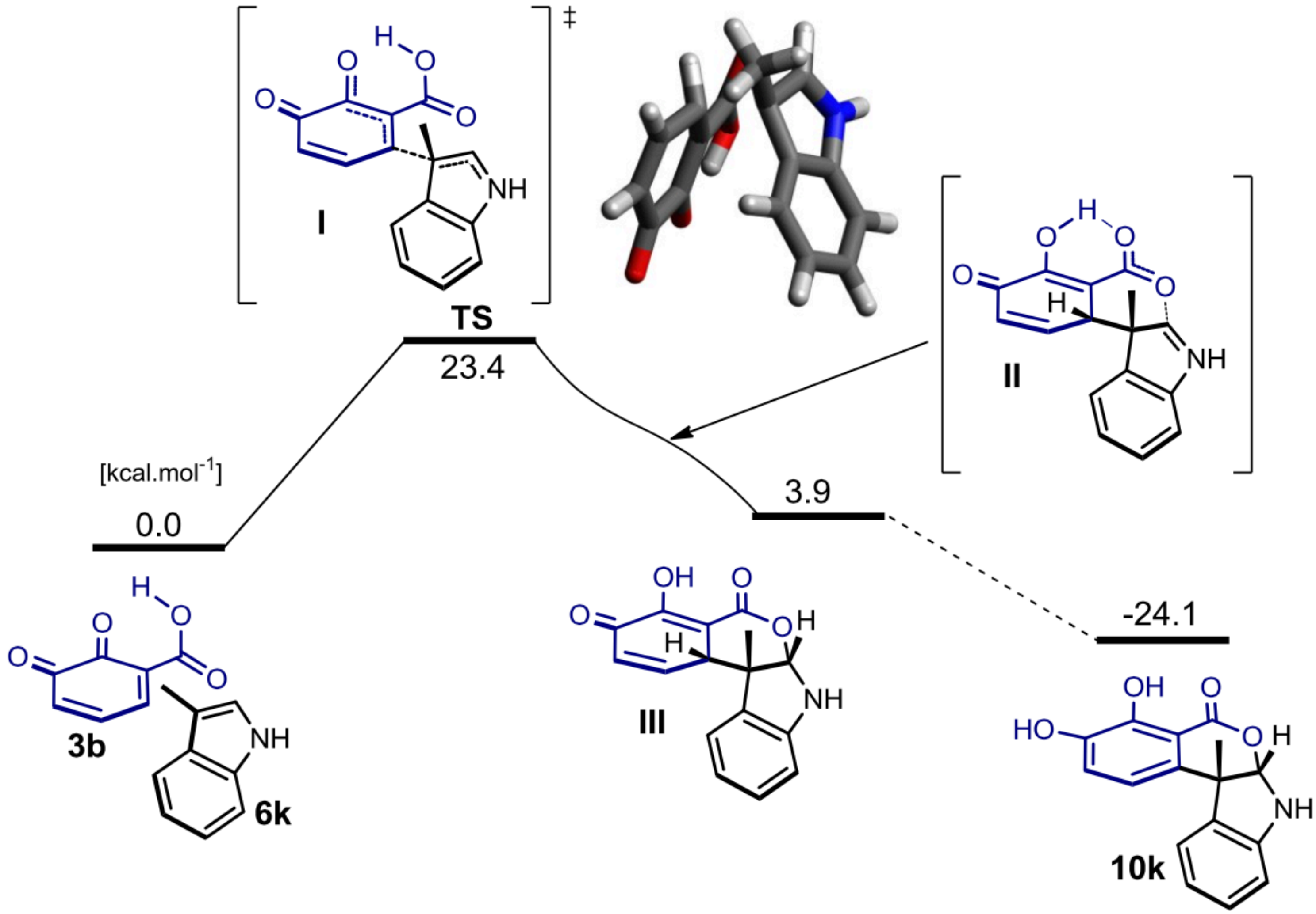


- B3LYP/6-31G* calculations used to locate transition states
- Considered three reaction pathways:
  1) stepwise reaction: anchoring, trapping
  2) concerted, synchronous: [4+2], tautomerization
  3) concerted, asynchronous: sequential 'events', tautomerization

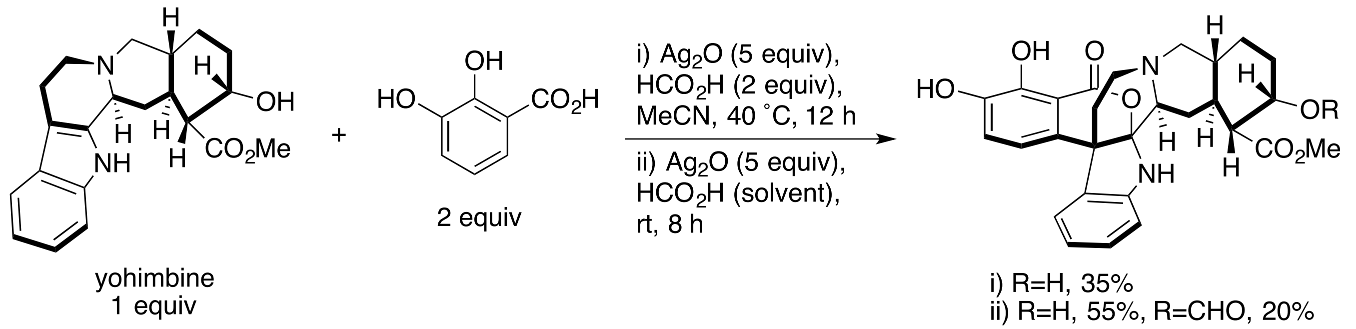


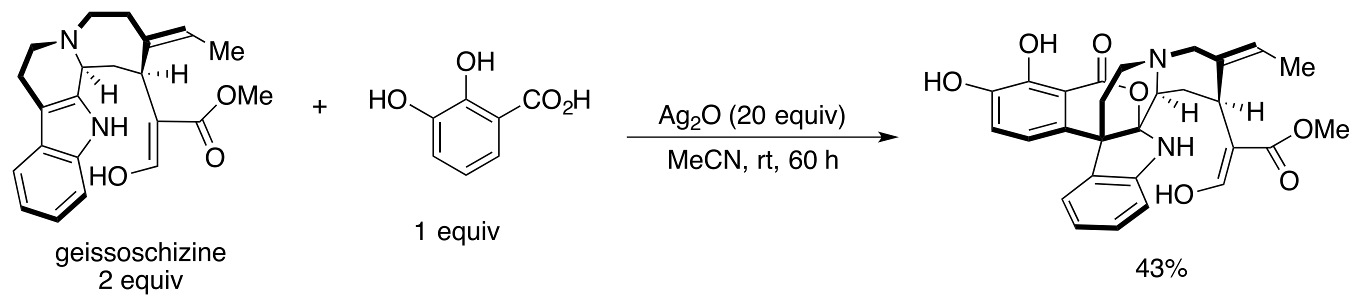
Mechanism – Calculations II

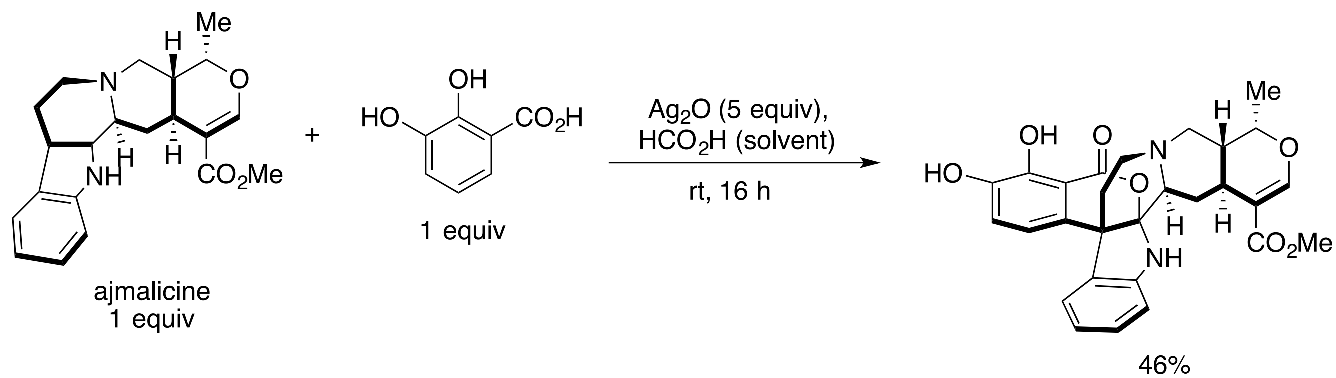
concerted, asynchronous



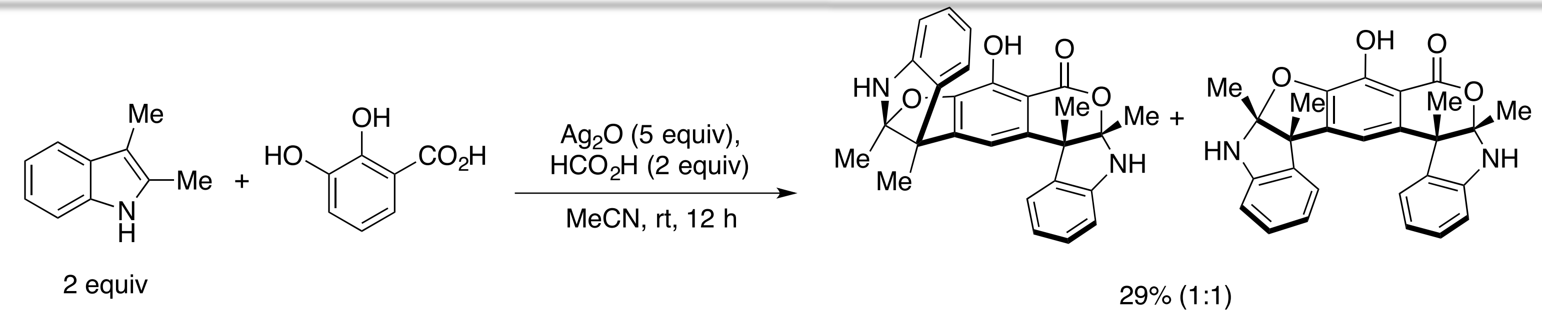
Increasing complexity with natural substances

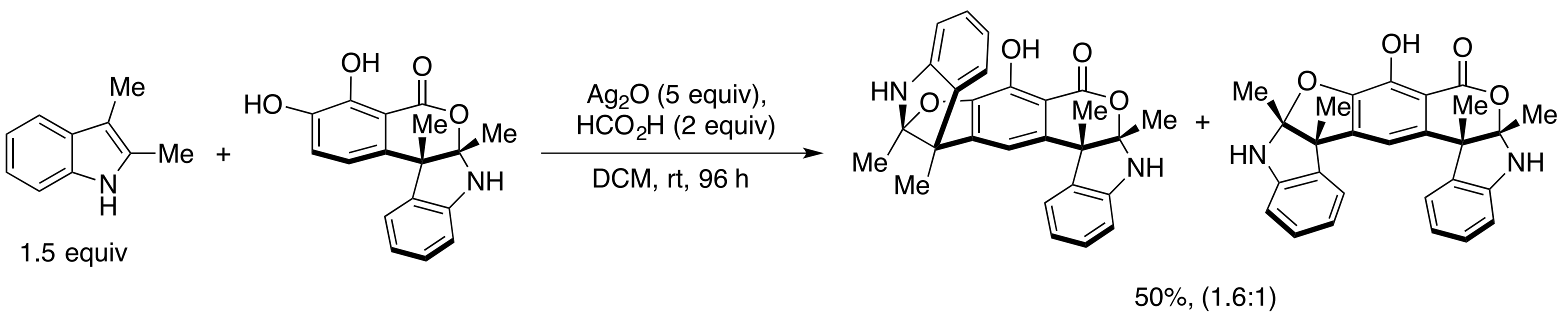


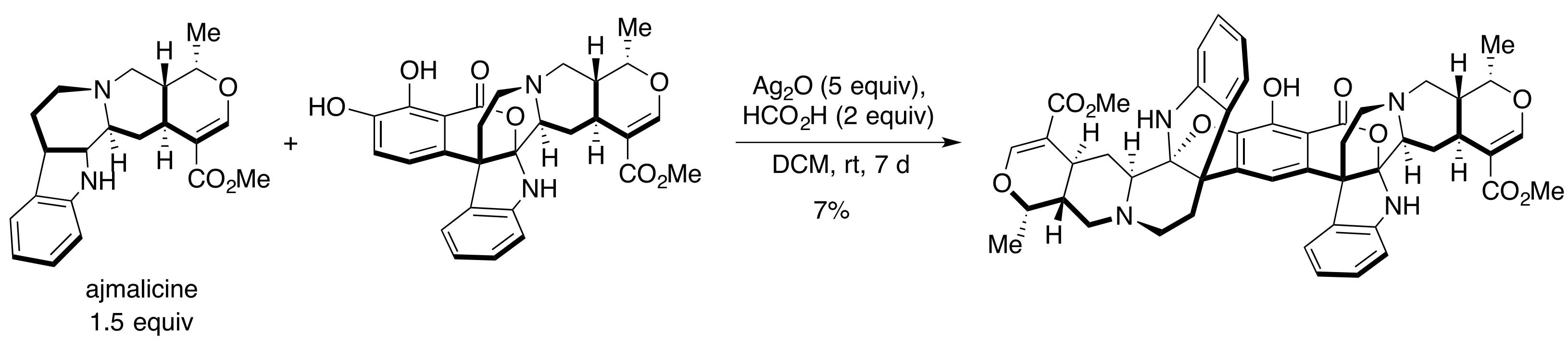




Double and sequential anchoring







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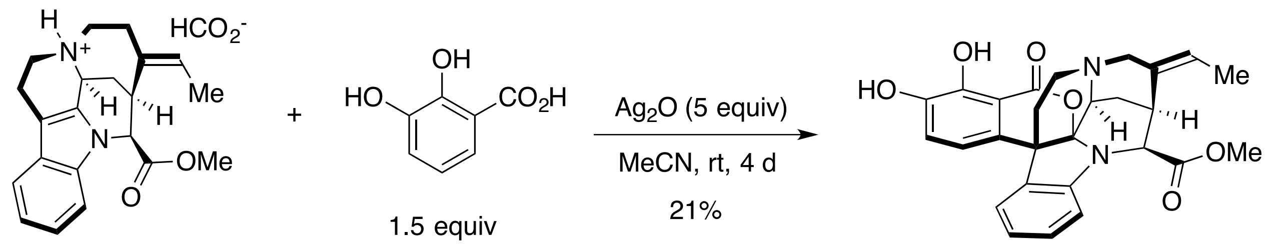
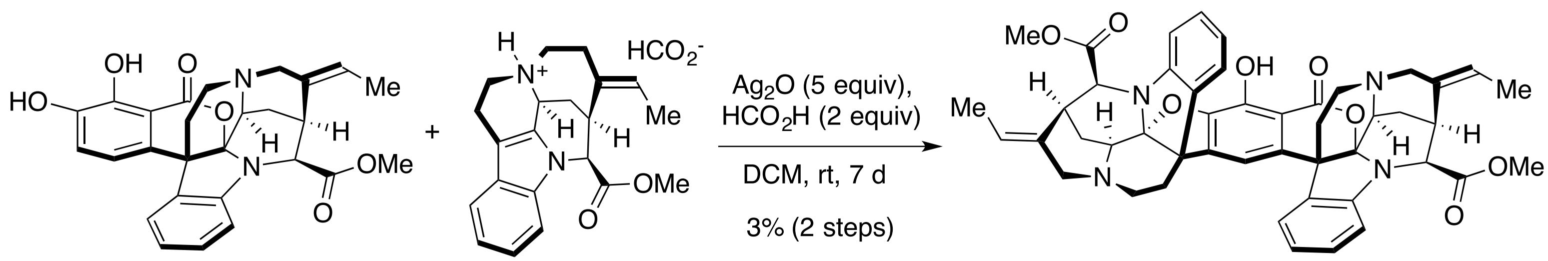
Synthesis of voacalgine A, bipleiophylline



pleiocarpamine formate
(0.007% from *Alstonia balansae)*

voacalgine A (revised structure)



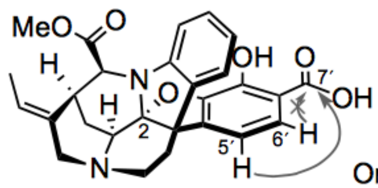
1.2 equiv

bipleiophylline

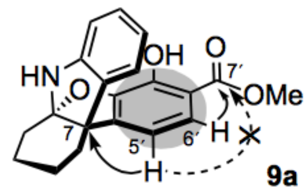
Conclusions

- An oxidative coupling protocol between indole and 2,3-dihydroxybenzoic acid was developed
- The first syntheses of bipleiophylline and voacalgine A were achieved
- The structure of voacalgine A was corrected and revised

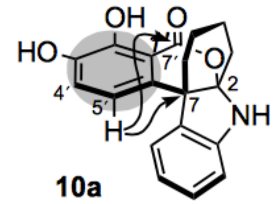
Voacalgine A Revision



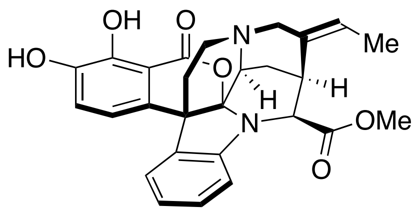
Voacalgine A
Original structure (**4**)



9a



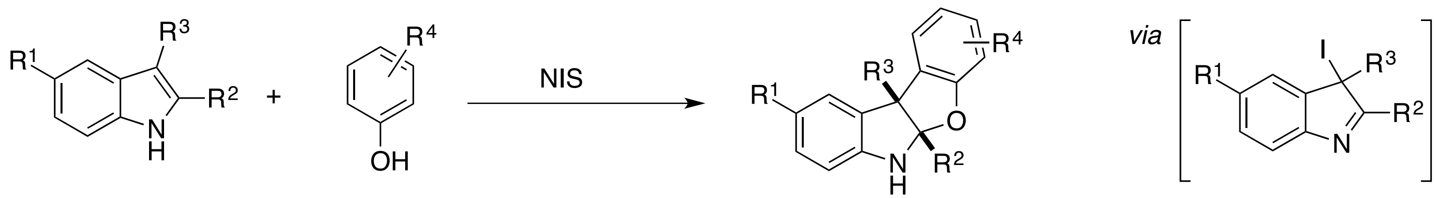
10a



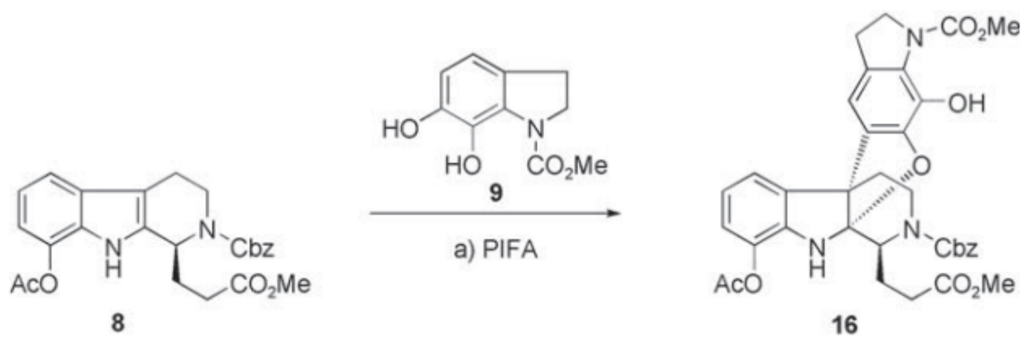
voacalgine A (revised structure)

15

Misc. Rxns



Org. Lett. **2014**, *16*, 5752–55.



Angew. Chem. Int. Ed. **2009***, 48*, 7616–7620.

Chem. Commun. **2015***, 51*, 1461–64.