Chemical Reactions of Indole Alkaloids That Enable Rapid Access to New Scaffolds for Discovery

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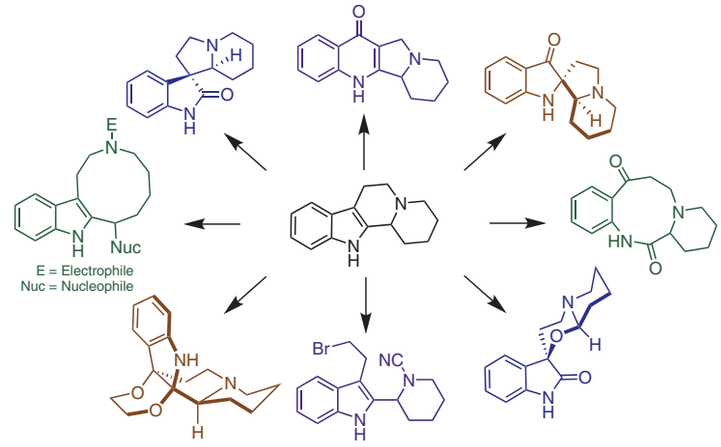

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Crowd-Reviewed

Abstract This graphical review provides a concise overview of indole alkaloids and chemical reactions that have been reported to transform both these natural products and derivatives to rapidly access new molecular scaffolds. Select biologically active compounds from these synthetic efforts are reported herein.

Keywords indole alkaloids, yohimbine, vincamine, reserpine, chemical synthesis, ring distortion

Natural products have played an essential role in medicine due to their abilities to bind to and modulate biological targets critical to disease. Vincristine, vancomycin, morphine, and paclitaxel are complex natural products with unique molecular architectures enabling exquisite drug–target interactions and therapeutic benefit to humankind. Many drug discovery programs have focused on utilizing synthetic chemistry to optimize the inherent biological activity, or pharmacology, of natural products as disease treatments; however, this graphical review focuses on synthetic transformations of indole alkaloids and relevant derivatives that would be expected to significantly alter, or re-engineer, their biological activity profiles.

Our group is developing a ring distortion platform to re-engineer the biological activities of readily available indole alkaloids using a combination of ring cleavage, ring rearrangement, and ring fusion reactions to rapidly generate diverse collections of small molecules bearing high stereochemical complexity. We hypothesize that dramatically altering the inherently complex molecular architectures of indole alkaloids will lead to new biologically active small molecules with activity profiles distinct from the parent indole alkaloid and alternative derivatives with diverse scaffolds.

Upon scanning the literature, one can find a diversity of exciting synthetic transformations that have been applied to numerous indole alkaloids and related indole-based molecules. Although these transformations have been used in total synthesis or methodology development, we view these precedented reactions as potential launching points for ring distortion chemistry. The overarching goals of this graphical review are to provide an overview of useful synthetic transformations of indole alkaloids (and related derivatives) by reaction type and for select indole alkaloids (e.g., yohimbine, vincamine).

This graphical review will begin with some basic background information related to a diversity of biologically active indole alkaloids (there are also many synthetic indole compounds of therapeutic utility in significant disease areas). Then, we will transition the graphical review to published ring cleavage and ring rearrangement transformations on indole alkaloids and derivatives. Finally, we will focus on reported transformations of select indole alkaloids (e.g., yohimbine, reserpine, catharanthine) that have been used, or could be useful, to generate novel scaffolds for drug discovery and chemical biology.

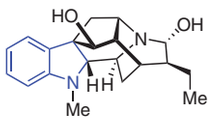
Biographical Sketches

Derek A. Leas was born and raised in Omaha, Nebraska, USA, where he earned a B.Sc. in medicinal chemistry from the University of Nebraska at Omaha (UNO) in 2014. In 2015, he joined the lab of Prof. Jonathan Vennerstrom at the University of Nebraska Medical Center, where his research focused on the synthesis of novel small molecules for the treatment of the tropical parasitic diseases schistosomiasis and malaria. He obtained his Ph.D. in pharmaceutical sciences in 2020 and joined the group of Prof. Robert Huigens at the University of Florida later that year as a postdoctoral associate, synthesizing complex and diverse compounds from indole alkaloids using various ring cleavage and ring fusion methods.

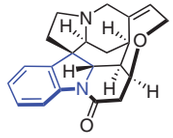
Daniel Schultz was raised in Orlando, Florida, USA and earned a B.Sc. in mechanical engineering and a B.Sc. in chemistry from the Florida Institute of Technology (USA) in 2017, the latter of which occurred under the mentorship of Prof. Alan Brown, whose research focuses on physical organic chemistry. Later that year, he joined the lab of Prof. Chenglong Li at the University of Florida, where his research involved computer-aided, structure-based drug design and the synthesis of novel protein–protein interaction inhibitors. He obtained his Ph.D. in medicinal chemistry in 2022, and joined the group of Prof. Robert Huigens at the University of Florida later that year as a postdoctoral associate.

Robert Huigens received his Ph.D. in chemistry with Prof. Christian Melander at North Carolina State University in 2009. He subsequently moved to the University of Illinois at Urbana-Champaign under the guidance of Prof. Paul Hergenrother, where he was as an American Cancer Society Postdoctoral Fellow. In 2013, he began his independent career as an assistant professor at the University of Florida where he was then promoted to associate professor of medicinal chemistry in 2020. The Huigens laboratory focuses on the utilization of available complex indole alkaloids to access diverse small molecules for drug discovery and the discovery of novel bacterial biofilm-eradicating agents inspired by natural products.

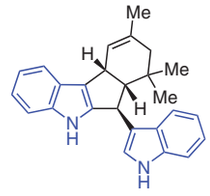
Indole Alkaloids: Their Biological Activities & Clinical Applications



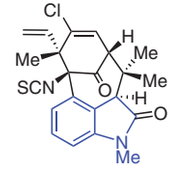
Ajmaline
arrhythmias



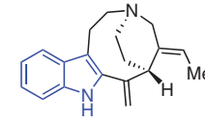
Strychnine*
glycine receptor
neurotoxin



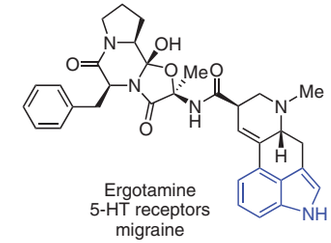
Yuehchukene
anti-fertility activity



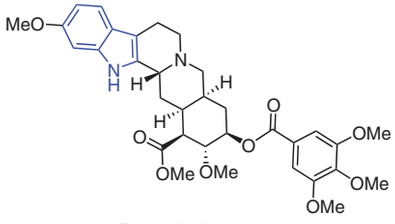
N-Methylwelwitindolinone C
isothiocyanate
cancer (P-glycoprotein)



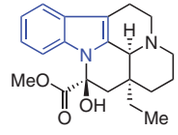
Pericine
mu-opioid receptor
pain



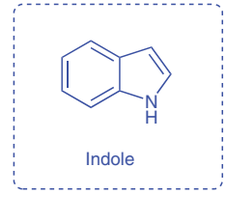
Ergotamine
5-HT receptors
migraine



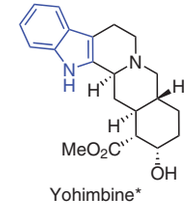
Reserpine*
vesicular monoamine transporter
hypertension



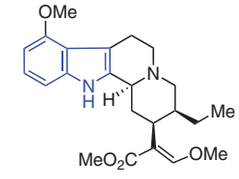
Vincamine*
cerebral vasodilation



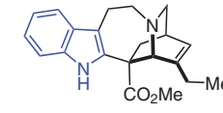
Indole



Yohimbine*
α_2-adrenergic receptor
antagonist; aphrodisiac



Mitragynine*
mu-opioid receptor
pain

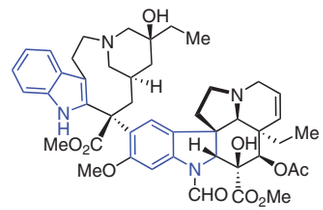


Catharanthine*
hypertension

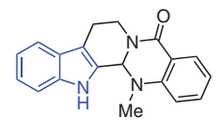
Further Reading:

(1a) O'Connor, *Nat. Prod. Rep.* **2006**, *23*, 532.
(1b) Hamann, *Chem. Rev.* **2010**, *110*, 4489.
(1c) Stöckigt, *Angew. Chem. Int. Ed.* **2011**, *50*, 8538.
(1d) Boger, *Acc. Chem. Res.* **2015**, *48*, 653.
(1e) Boger, *Proc. Natl. Acad. Sci. U.S.A.* **2016**, *113*, 9691.
(1f) Huigens, *ChemBioChem* **2019**, *20*, 2273.

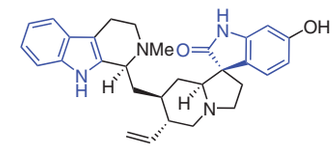
* Commercially/synthetically accessible (gram-scale)



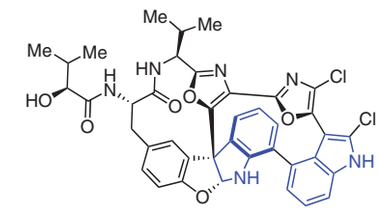
Vincristine
β-tubulin
cancer



(±)-Evodiamine*
stimulant
anti-obesity



Strychnofoline
inhibits mitosis
cancer



Diazonamide A
ornithine δ-amino transferase
cancer (inhibits mitotic function)

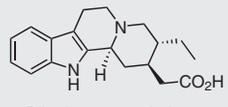
Figure 1 Select indole alkaloids, their biological activities and clinical applications[1a–f]

Indole-Promoted C–N Ring Cleavage Reactions Employing Chloroformates and Related Electrophiles (Part 1)

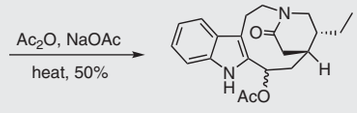
Notable Features:

- Access to diverse compounds through chloroformate and nucleophile selection
- Can incorporate diverse nucleophiles (e.g., alcohols, hydrides, carboxylates, cyanides, amines)

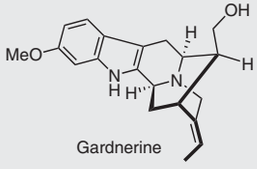
Seminal Studies:



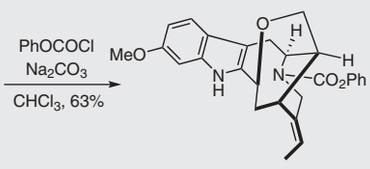
Dihydrocorynantheine Derivative



(2a) Dolby, *J. Am. Chem. Soc.* **1964**, *86,* 1890.

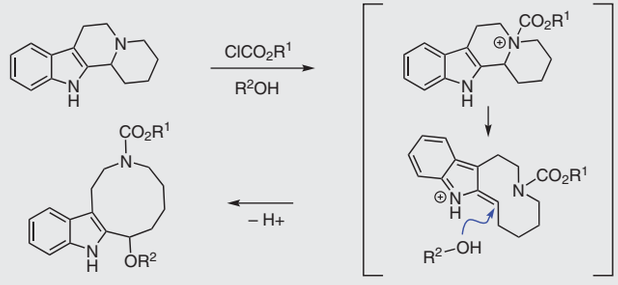


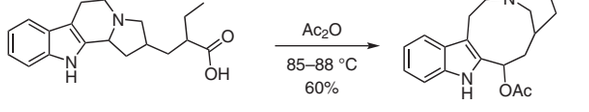
Gardnerine



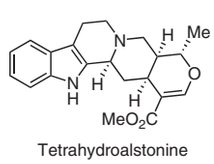
(2b) Sakai, *Yakugaku Zasshi* **1973**, *93,* 1165.

Chloroformate-Mediated Indole-Promoted Ring Cleavage Mechanism:

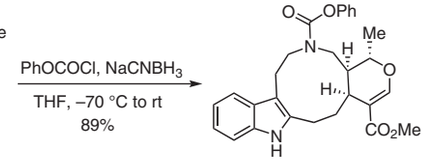


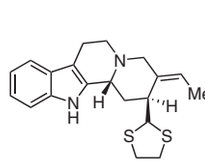


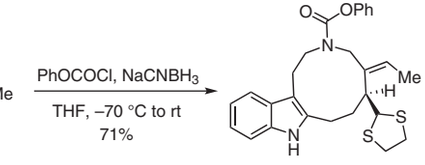
(2c) Atta-Ur-Rahman, *Tetrahedron* **1980**, *36,* 1057.



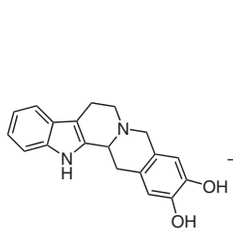
Tetrahydroalstonine

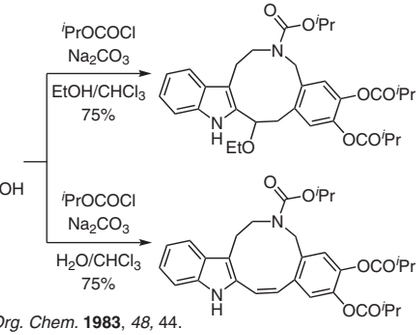




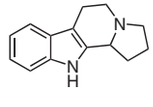


(2d) Calverly, *J. Chem. Soc., Chem. Commun.* **1981**, 1209.

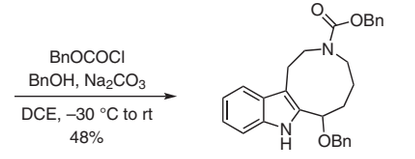




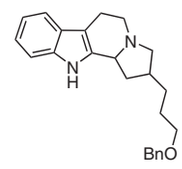
(2e) Liu, *J. Org. Chem.* **1983**, *48,* 44.

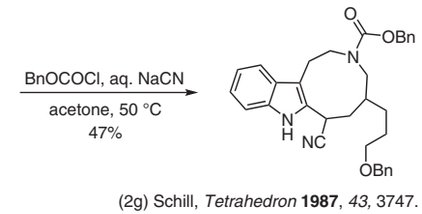


(±)-Harmicine

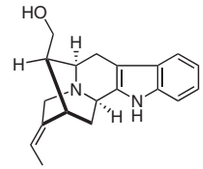


(2f) Schill, *Tetrahedron* **1987**, *43,* 3729.

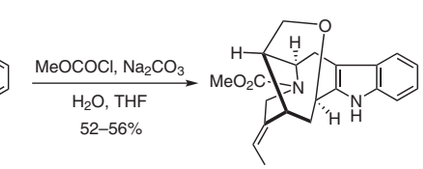




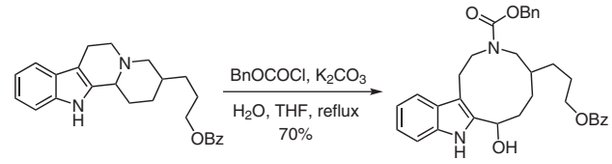
(2g) Schill, *Tetrahedron* **1987**, *43,* 3747.



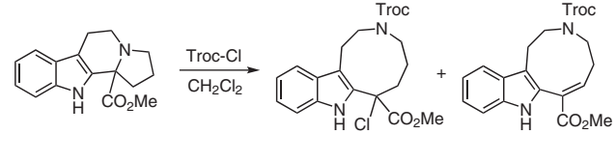
(+)-Koumidine



(2h) Magnus *J. Am. Chem. Soc.* **1990**, *112,* 5220.
See also: (2i) Magnus *J. Am. Chem. Soc.* **1989**, *111,* 786.



(2j) Schill, *Tetrahedron* **1990**, *46,* 1211.



Small Scale: 3 g
Large Scale: 49 g

79%
50%

10%
27%

(2k) Magnus, *J. Am. Chem. Soc.* **1993**, *115,* 8116.

Further Reading:

(2l) Foster, *Chem. Commun.* **1967**, 21.
(2m) Sakai, *Heterocycles* **1976**, *4,* 981.
(2n) Harley-Mason, *Tetrahedron Lett.* **1981**, *22,* 1631.
(2o) Harley-Mason, *Tetrahedron* **1981**, *37,* 1547.
(2p) Calverly, *J. Chem. Res., Miniprint* **1983**, *8,* 1848.
(2q) Schill, *Helv. Chim. Acta* **1986**, *69,* 438.
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(2s) Sakai, *Tetrahedron* **1989**, *45,* 1327.
(2t) Sakai, *J. Chem. Soc., Perkin Trans. 1* **1989**, 1075.
(2u) Sakai, *Tetrahedron Lett.* **1990**, *31,* 5483.
(2v) Mahboobi, *Arch. Pharm.* **1994**, *327,* 463.
(2w) Bonjoch, *J. Chem. Soc., Chem. Commun.* **1995**, 2317.
(2x) Bonjoch, *J. Org. Chem.* **1998**, *63,* 7338.
(2y) Magnus, *Tetrahedron Lett.* **1999**, *40,* 5135.
(2z) Magnus, *Tetrahedron* **2002**, *58,* 3423.
(2aa) Seo, *Nat. Commun.* **2020**, *11,* 4761.

Figure 2 Indole-promoted C–N ring cleavage reactions employing chloroformates and related electrophiles (Part 1)[2a–2aa]

Indole-Promoted C–N Ring Cleavage Reactions Employing Chloroformates and Related Electrophiles (Part 2)

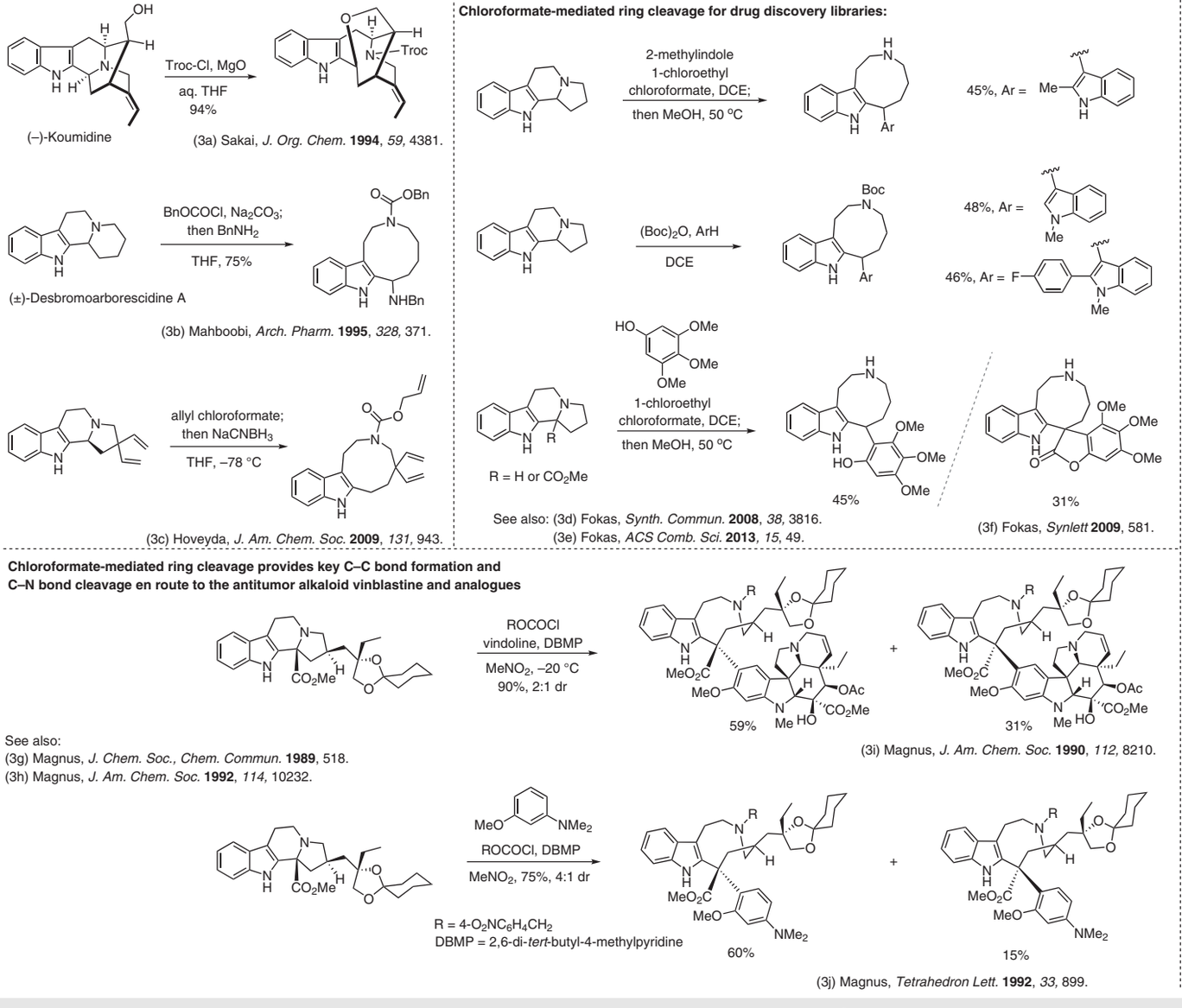


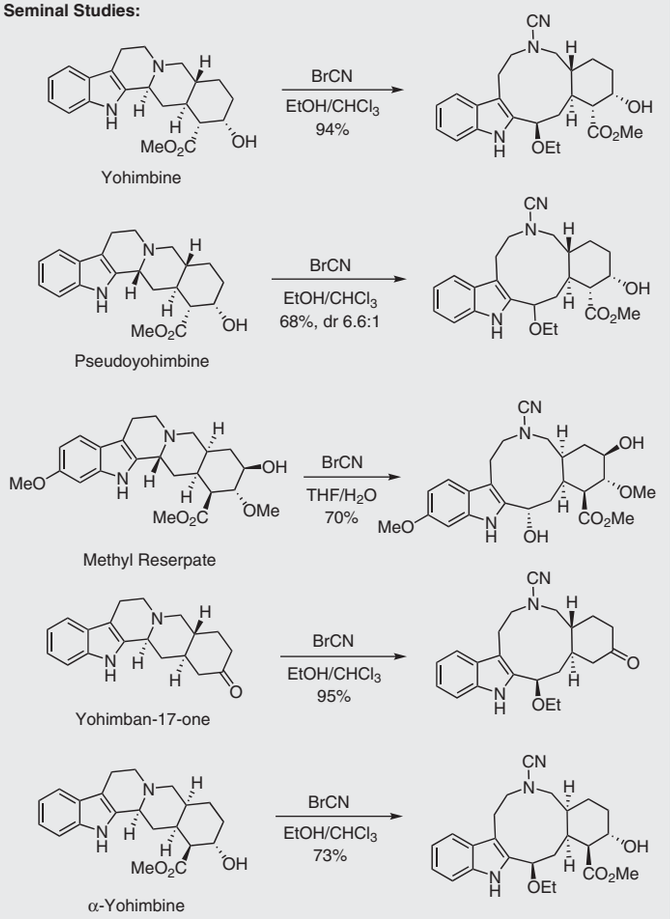
Figure 3 Indole-promoted C–N ring cleavage reactions employing chloroformates and related electrophiles (Part 2)[3a–o]

Indole-Promoted C–N Ring Cleavage Reactions Using the von Braun Reaction (Part 1)

Notable Features of Indole Alkaloid von Braun Chemistry:

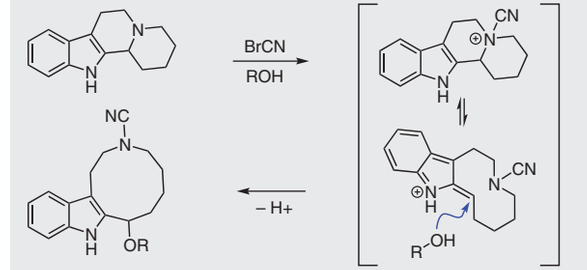
- Generally diastereoselective (inversion product preferred)
- Water, alcohols, cyanide used as nucleophiles

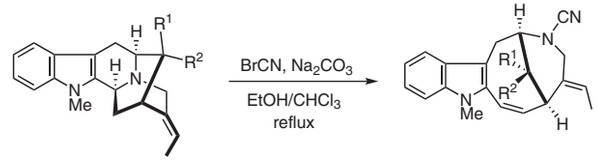
Seminal Studies:



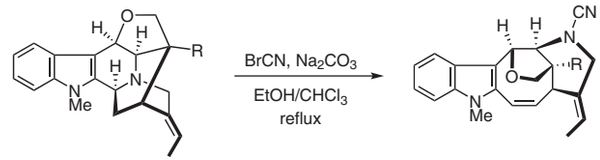
(4a) Albright, *J. Am. Chem. Soc.* **1969**, *91*, 4317.

Indole-Promoted von Braun Reaction Mechanism:

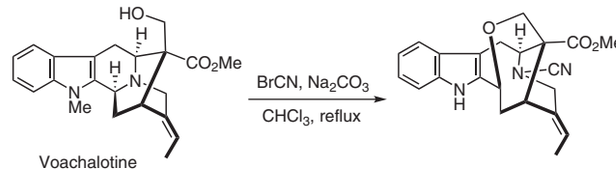




(+)-Na-Methylpericyclivine: R^1 = H, R^2 = CO_2Me
O-Acetyl Voachalotine: R^1 = CH_2OAc, R^2 = CO_2Me

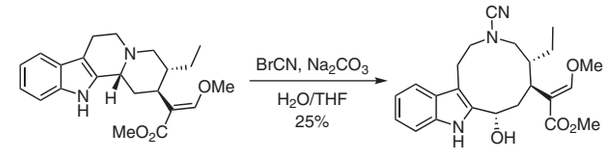


(+)-Dehydrovoachalotine

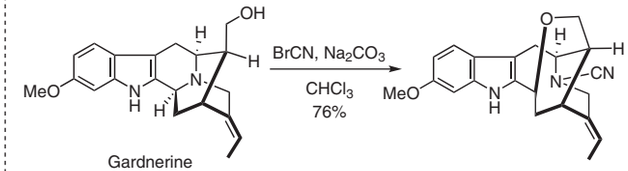


Voachalotine

(4b) Lampe-Tirions, *Bull. Soc. Chim. Belges* **1971**, *80*, 27.

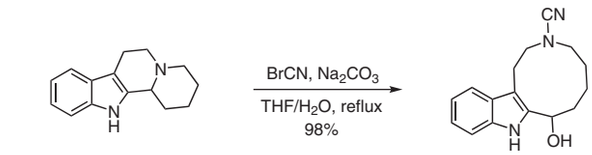


Hirsutine



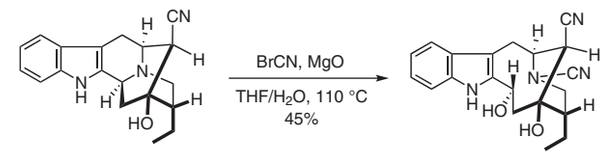
Gardnerine

(2b) Sakai, *Yakugaku Zasshi* **1973**, *93*, 1165.



(±)-Desbromoarborescidine A

(4c) Husson, *Tetrahedron* **1977**, *33*, 315.



(4d) Kutney, *J. Am. Chem. Soc.* **1978**, *100*, 938.

Further Reading:

(2n) Harley-Mason, *Tetrahedron Lett.* **1981**, *22*, 1631.
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(4f) Sakai, *Chem. Pharm. Bull.* **1980**, *28*, 3454.
(4g) Sakai, *Heterocycles* **1980**, *14*, 85.
(4h) Sakai, *Heterocycles* **1987**, *26*, 1211.
(4i) Sakai, *Chem. Pharm. Bull.* **1991**, *39*, 1677.

Figure 4 Indole-promoted C–N cleavage reactions using the von Braun reaction (Part 1)[2b,n,4a–i]

Indole-Promoted C–N Ring Cleavage Reactions Using the von Braun Reaction (Part 2)

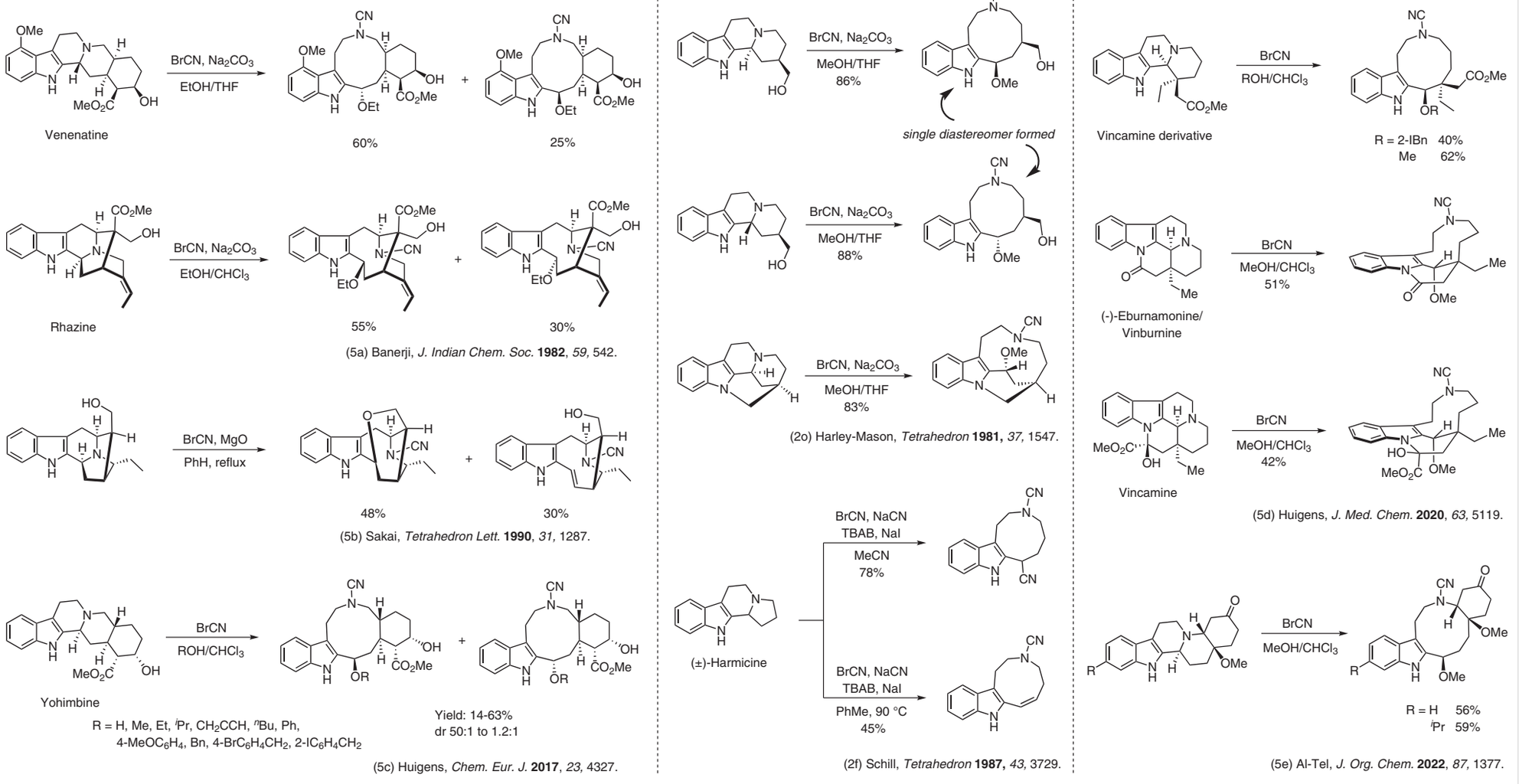


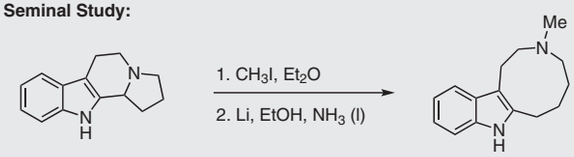
Figure 5 Indole-promoted C–N cleavage reactions using the von Braun reaction (Part 2)[2f,o,5a–e]

Indole-Promoted Birch Ring Cleavage Reactions

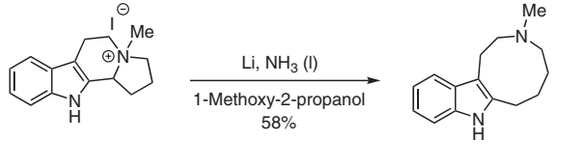
Notable Features:

- Employs a variety of quaternary ammonium salts

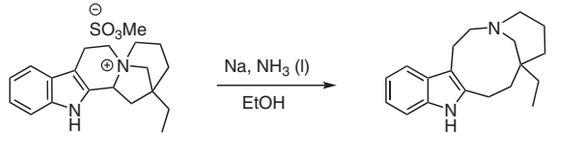
Seminal Study:



(6a) Wenkert, *Can. J. Chem.* **1964**, *42,* 489.

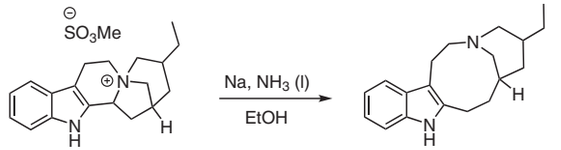


(6b) Herbst, *J. Med. Chem.* **1966**, *9,* 864.



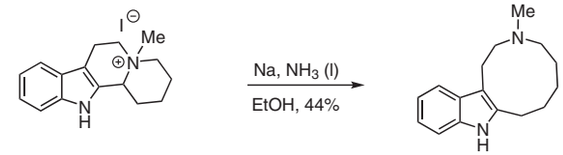
(±)-Quebrachamine

(6c) Kutney, *J. Am. Chem. Soc.* **1966**, *88,* 3656.

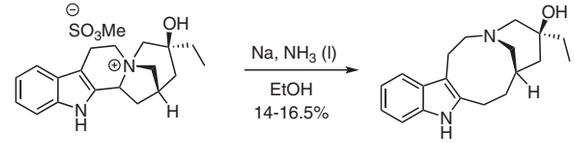


(±)-Dihydrocleavamine

(6d) Kutney, *J. Am. Chem. Soc.* **1966**, *88,* 4756.
(6e) Harley-Mason, *Chem. Commun.* **1966**, *20,* 743.

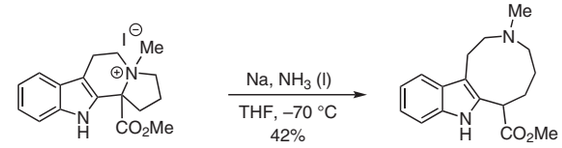


(6f) Dolby, *J. Org. Chem.* **1967**, *32,* 1391.

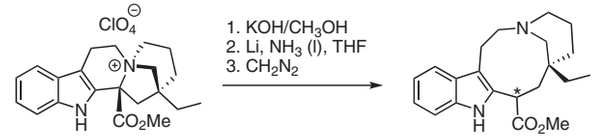


(±)-Velbanamine

(6g) Takano, *J. Org. Chem.* **1980**, *45,* 3729.

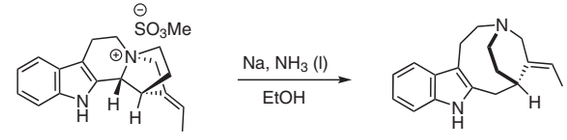


(6h) Lévy, *Bull. Soc. Chim. Fr.* **1981**, *2,* 179.

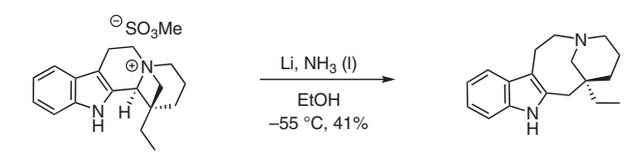


R: (±)-Epivincadine 66%
S: (±)-Vincadine 7%

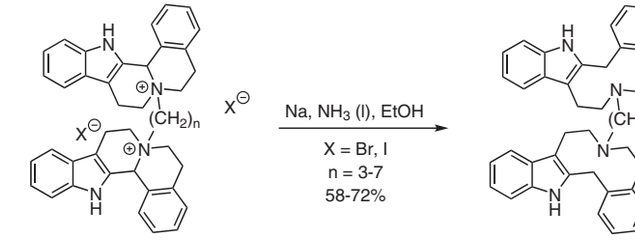
(6i) Wenkert, *Tetrahedron* **1981**, *37,* 4017.



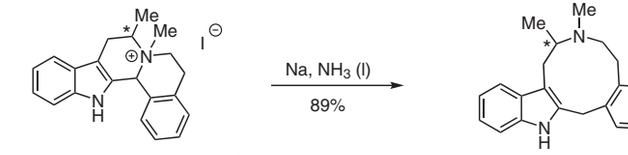
(6j) Takano, *Tetrahedron Lett.* **1982**, *23,* 881.



(6k) Szántay, *J. Org. Chem.* **1985**, *50,* 3760.



(6l) Lehmann, *Arch. Pharm.* **2002**, *335,* 367.



**S enantiomer 100-fold more active than R enantiomer against dopamine receptors*

(6m) Lehmann, *J. Med. Chem.* **2011**, *54,* 7422.

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(6o) Takano, *J. Chem. Soc., Chem. Commun.* **1980**, 616.
(6p) Atta-ur-Rahman, *Tetrahedron* **1980**, *36,* 1063.
(6q) Takano, *Tetrahedron Lett.* **1980**, *21,* 3697.
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(6t) Fuji, *J. Org. Chem.* **1990**, *55,* 517.
(6u) Andersson, *J. Org. Chem.* **1998**, *63,* 6007.
(6v) Lehmann, *J. Med. Chem.* **2000**, *43,* 2079.
(6w) Lehmann, *Arch. Pharm.* **2001**, *334,* 241.
(6x) Ogasawara, *Tetrahedron Lett.* **2001**, *42,* 7311.
(6y) Ohsaki, *J. Org. Chem.* **2002**, *67,* 6449.
(6z) Lehmann, *J. Med. Chem.* **2006**, *49,* 760.
(6aa) Lehmann, *Bioorg. Med. Chem. Lett.* **2007**, *17,* 1399.
(6ab) Enzensperger, *Arch. Pharm.* **2010**, *344,* 28.

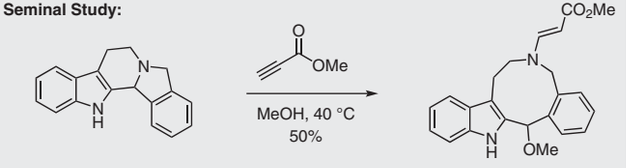
Figure 6 Indole-promoted Birch ring cleavage reactions[6a–ab]

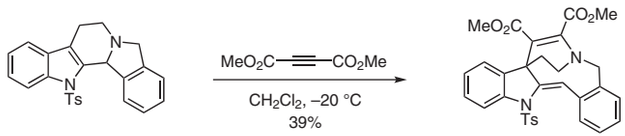
(A) Indole-Promoted C–N Ring Cleavage via Propiolates and Other Alkynes

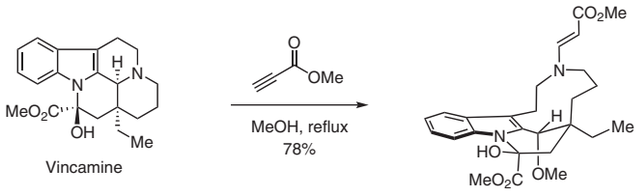
Notable Features:

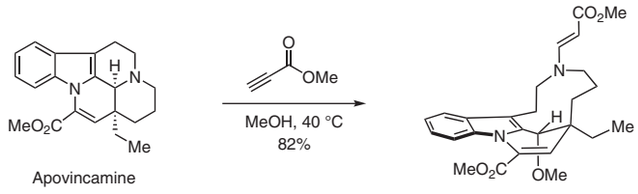
- Employs a variety of diverse substrates

Seminal Study:

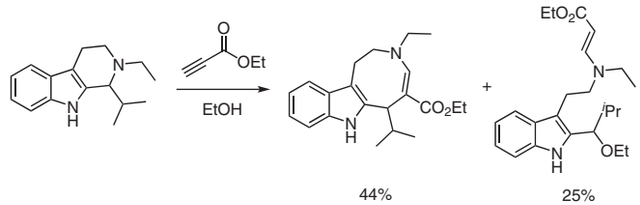




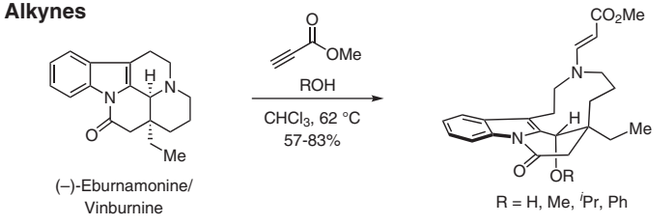


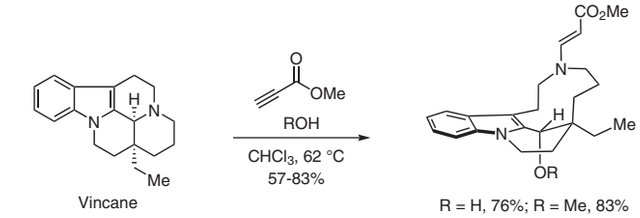


(7a) Voskressensky, *Russ. Chem. Bull.* **2012**, *61,* 1231.

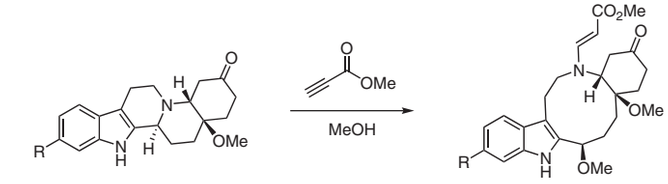


(7b) Voskressensky, *Eur. J. Org. Chem.* **2004**, *2004*, 3128.
(7c) Voskressensky, *Chem. Heterocycl. Compd.* **2007**, *43,* 587.



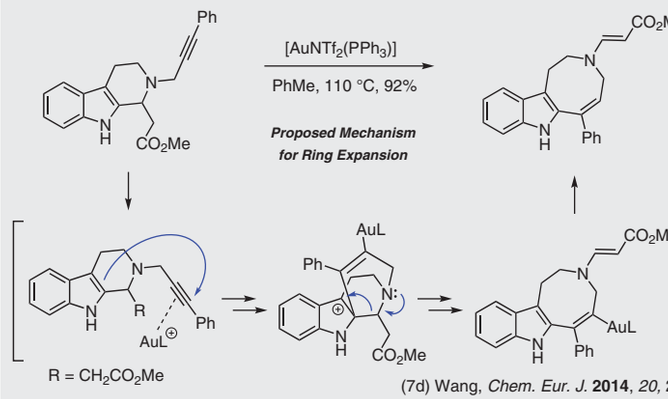


(5d) Huigens, *J. Med. Chem.* **2020**, *63,* 5119.



(5e) Al-Tel, *J. Org. Chem.* **2022**, *87,* 1377.

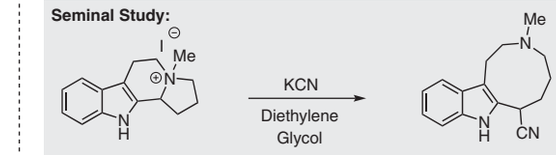
Gold(I)-Catalyzed Ring Expansion of 2-Propargyl-β-Tetrahydrocarboline



(7d) Wang, *Chem. Eur. J.* **2014**, *20,* 2925.

(B) Ring Cleavage of Quaternary Ammonium Salts (non-Birch Reaction)

Seminal Study:



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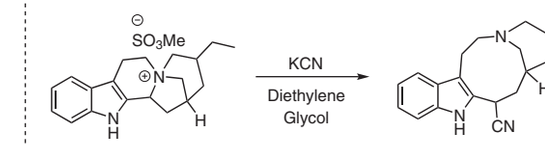

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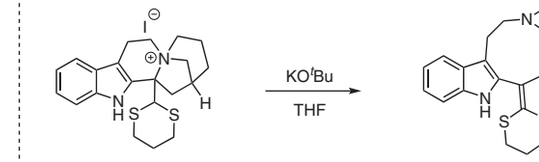

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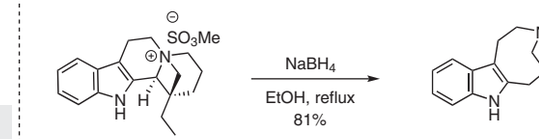
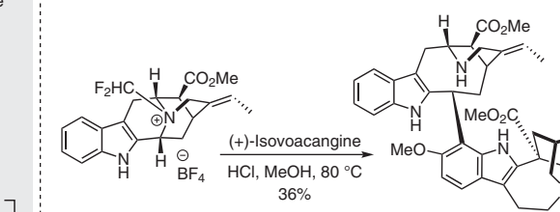


(6k) Szántay, *J. Org. Chem.* **1985**, *50,* 3760.



(7g) Han, *J. Am. Chem. Soc.* **2021**, *143,* 19966.

Further Reading:

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(6o) Takano, *J. Chem. Soc., Chem. Commun.* **1980**, 616.
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(7h) Bailey, *Tetrahedron Lett.* **1987**, *28,* 2879.
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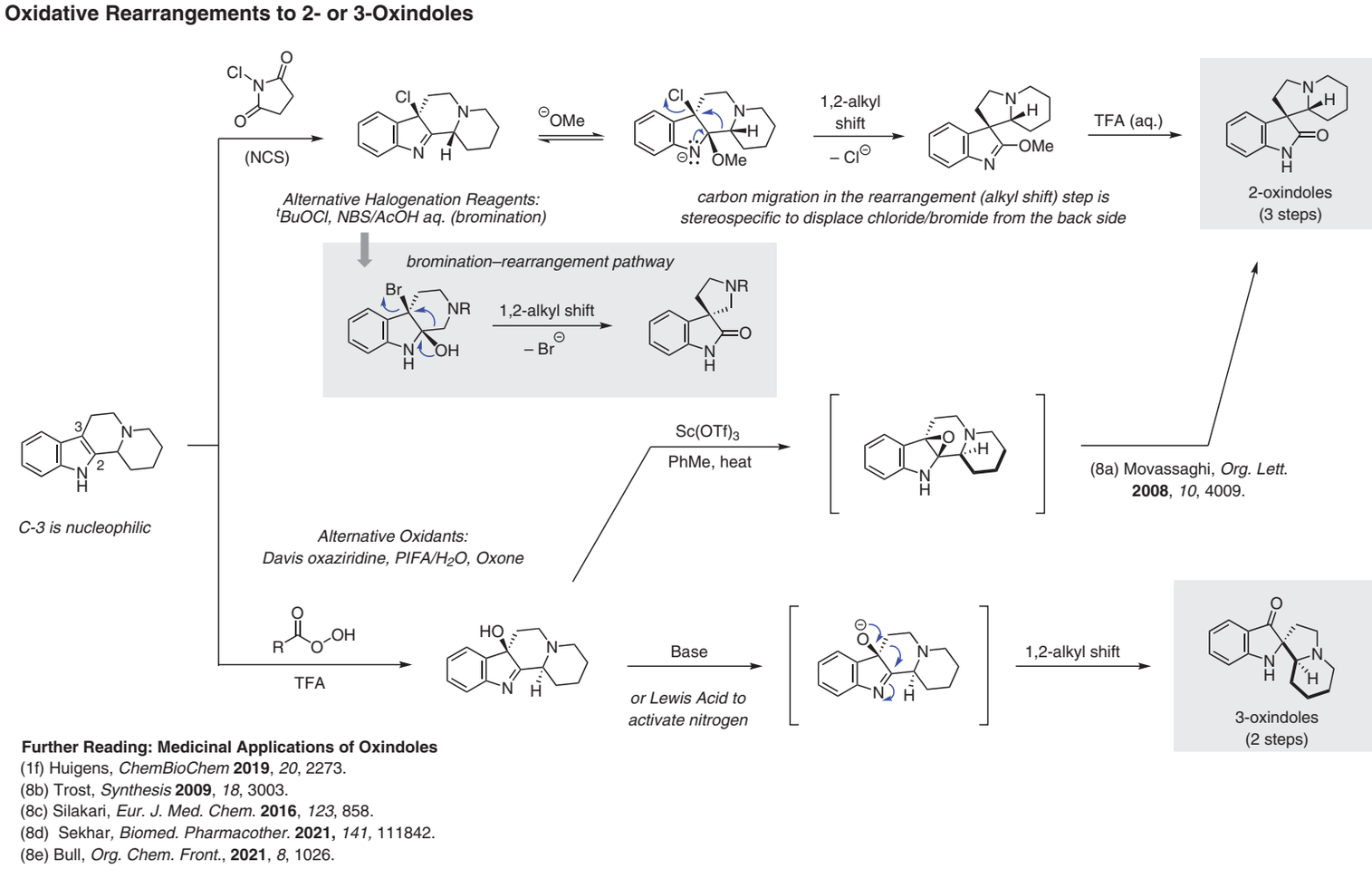
Figure 7 (A) Indole-promoted C–N ring cleavage via propiolates and other alkynes. (B) Ring cleavage of quaternary ammonium salts (non-Birch reaction).[2l,5d,e,6o–p,7a–i]



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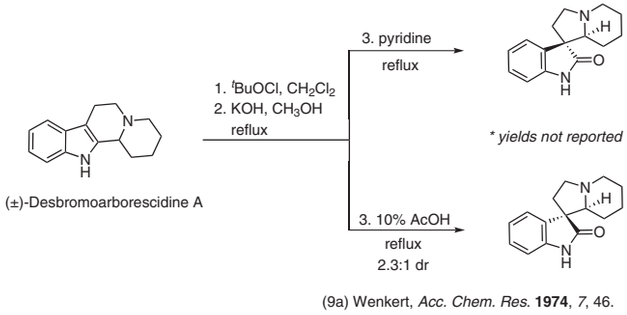
(8d) Sekhar, *Biomed. Pharmacother.* **2021**, *141*, 111842.
(8e) Bull, *Org. Chem. Front.*, **2021**, *8*, 1026.

Figure 8 Oxidative rearrangements to 2- or 3-oxindoles[1f,8a–e]

Reactions of Indole Alkaloids to Yield 2-Oxindole Derivatives via Ring Rearrangement



(±)-Desbromoarborescidine A

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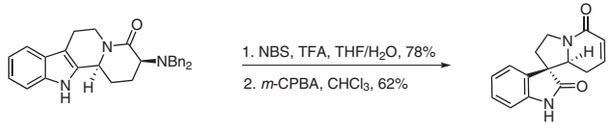
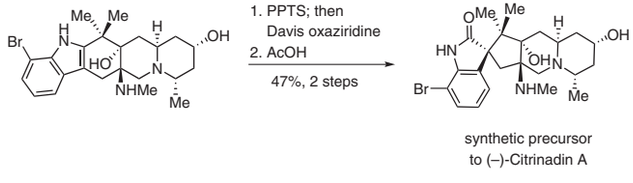
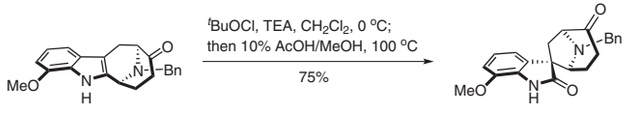


(9b) Thammapichai, *Tetrahedron* **2020**, *76*, 131261.



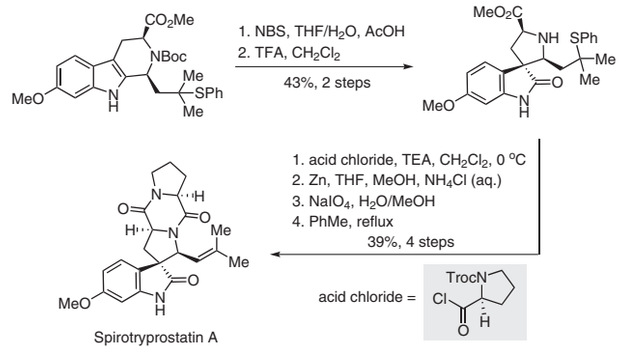
synthetic precursor
to (–)-Citrinadin A

(9c) Martin, *J. Am. Chem. Soc.* **2013**, *135*, 10886.



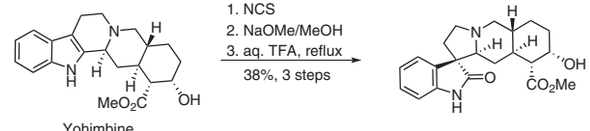
synthetic precursor to
(–)-Gardmultimine A

(9d) She, *Org. Lett.* **2020**, *22*, 2022.



Spirotryprostatin A

(9e) Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 2147.



Yohimbine

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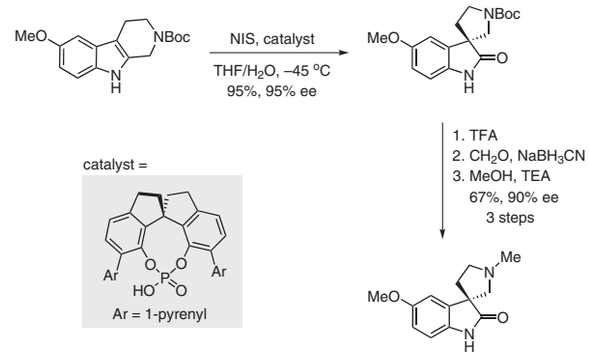
See also: (9f) Tong, *Nat. Commun.* **2019**, *10*, 4754.



(–)-Horsfiline

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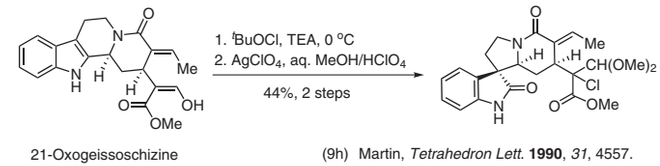
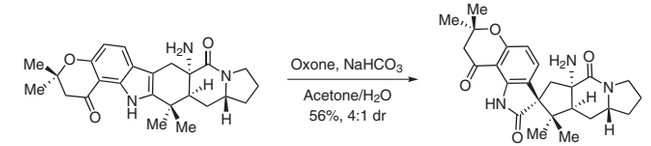


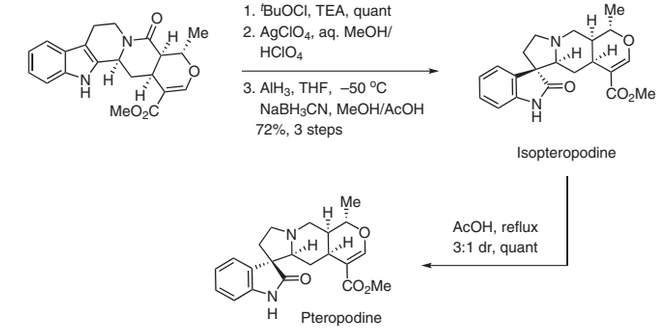
21-Oxogeissoschizine

(9h) Martin, *Tetrahedron Lett.* **1990**, *31*, 4557.



Cyclopiamine B congener

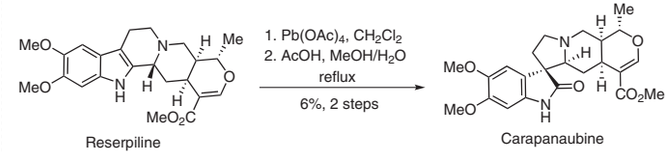
(9i) Sarpong, *Nature* **2014**, *509*, 318.



Isopteropodine

Pteropodine

(9h) Martin, *Tetrahedron Lett.* **1990**, *31*, 4557.



Reserpiline

Carapanaubine

(9j) Finch, *J. Am. Chem. Soc.* **1963**, *85*, 1520.

Figure 9 Reactions of indole alkaloids to yield 2-oxindole derivatives via ring rearrangement[5c,9a–j]

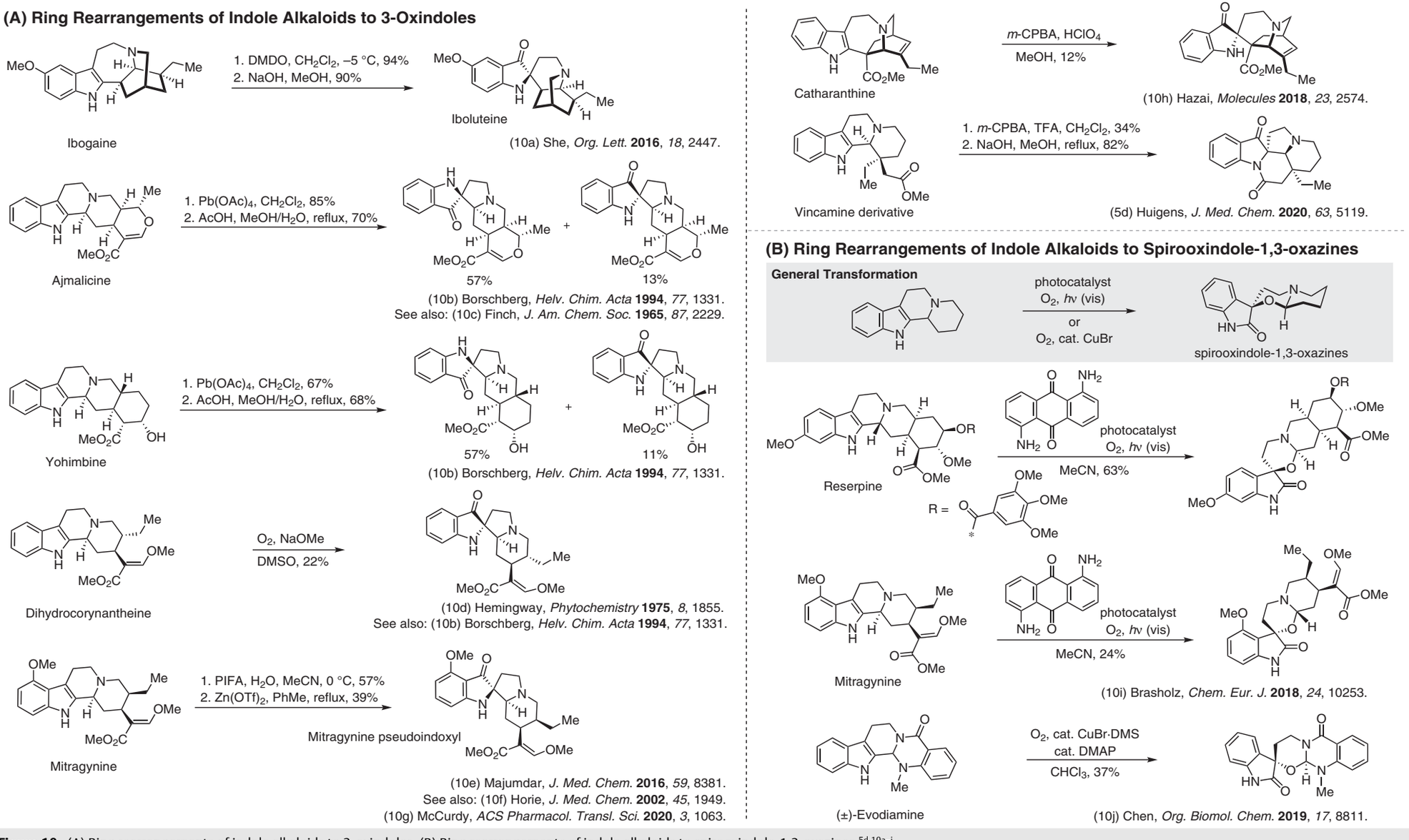


Figure 10 (A) Ring rearrangements of indole alkaloids to 3-oxindoles. (B) Ring rearrangements of indole alkaloids to spirooxindole-1,3-oxazines.[5d,10a–j]

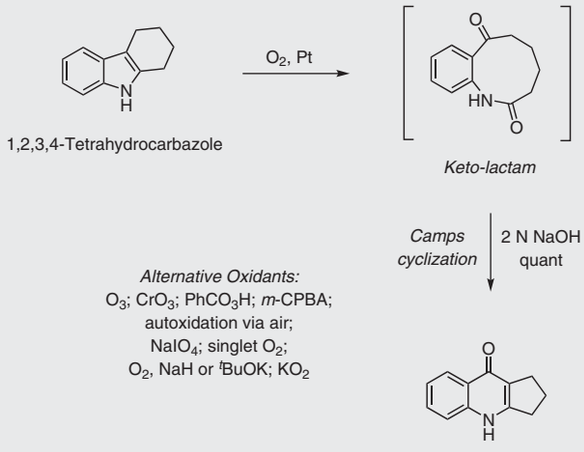
Oxidative Cleavage and Ring Rearrangement of Indole Alkaloids to Give Quinolones

Notable Features:

- Intermediate keto-lactam is isolatable in some cases
- Keto-lactam intermediates can undergo a transannular condensation in acid or base
- Generally these reactions are carried out in one pot

Seminal Study:

Witkop–Winterfeldt Oxidation



(11a) Witkop, *J. Am. Chem. Soc.* **1951**, *73*, 2641.

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Witkop–Winterfeldt oxidation and related review:
(11j) Roxburgh, *Tetrahedron* **1993**, *49*, 10749.
(11k) Breinbauer, C*urr. Org. Chem.* **2007**, *11*, 159.

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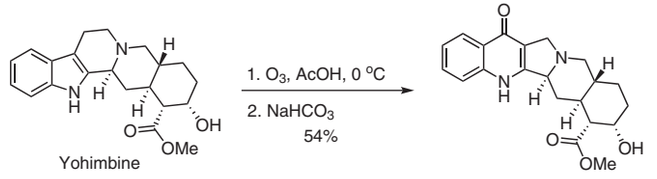
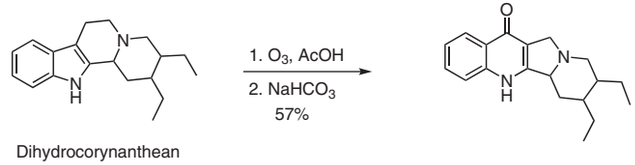
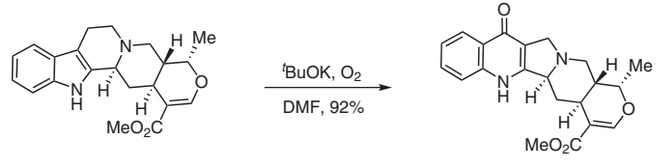
(9f) Tong, *Nat. Commun.* **2019**, *10*, 4754.
(11l) Husson, *Synlett* **1998**, 1071.
(11m) Sigaut, *Tetrahedron* **2000**, *56*, 9641.
(11n) Hammouda, Z. *Naturforsch.* **2009,** *64b*, 415.
(11o) Breinbauer, *Tetrahedron* **2011,** *67*, 965.
(11p) Kozmin, *J. Org. Chem.* **2013**, *78*, 8645.
(11q) Dai, *Org. Lett.* **2014**, *16*, 6216.
(11r) Wang, *Synthesis* **2018**, *50*, 2897.
(11s) Vennerstrom, *J. Org. Chem.* **2020**, *85*, 2846.



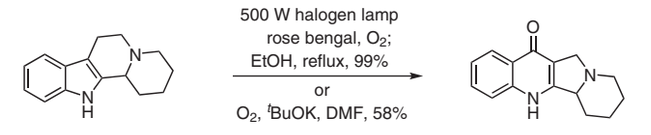
(11b) Witkop, *J. Am. Chem. Soc.* **1953**, *75*, 3371.



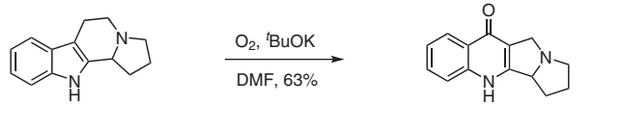
(11c) Prelog, *Helv. Chim. Acta* **1955**, *38*, 1073.



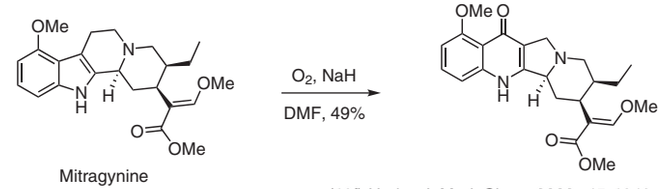
(11d) Winterfeldt, *Liebigs Ann. Chem.* **1971**, *745*, 23.



(11e) Nakagawa, *J. Chem. Soc., Chem. Commun.* **1982**, 742.
(11f) Husson, *Tetrahedron Lett.* **1997**, *38*, 2997.



(11f) Husson, *Tetrahedron Lett.* **1997**, *38*, 2997.



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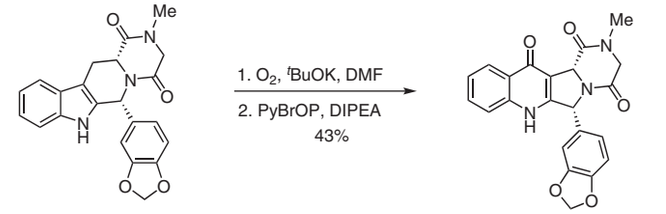

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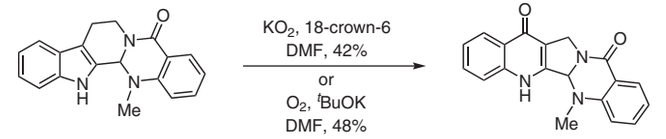

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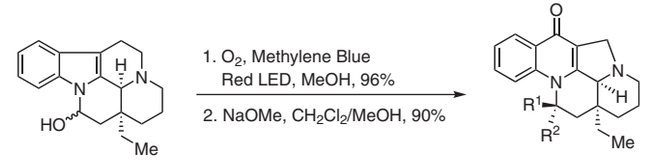
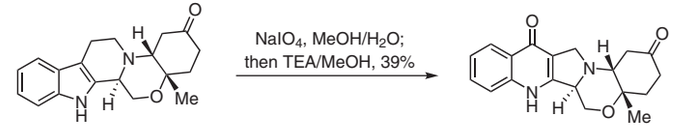


R1 = OH, R2 = H; R1 = H, R2 = OH (90%, 3:1 dr)
(11i) Westwood, *Org. Lett.* **2012**, *14*, 6166.



(5e) Al-Tel, *J. Org. Chem.* **2022**, *87*, 1377.

Figure 11 Oxidative cleavage and ring rearrangement of indole alkaloids to give quinolones[5e,9f,10f,11a–s]

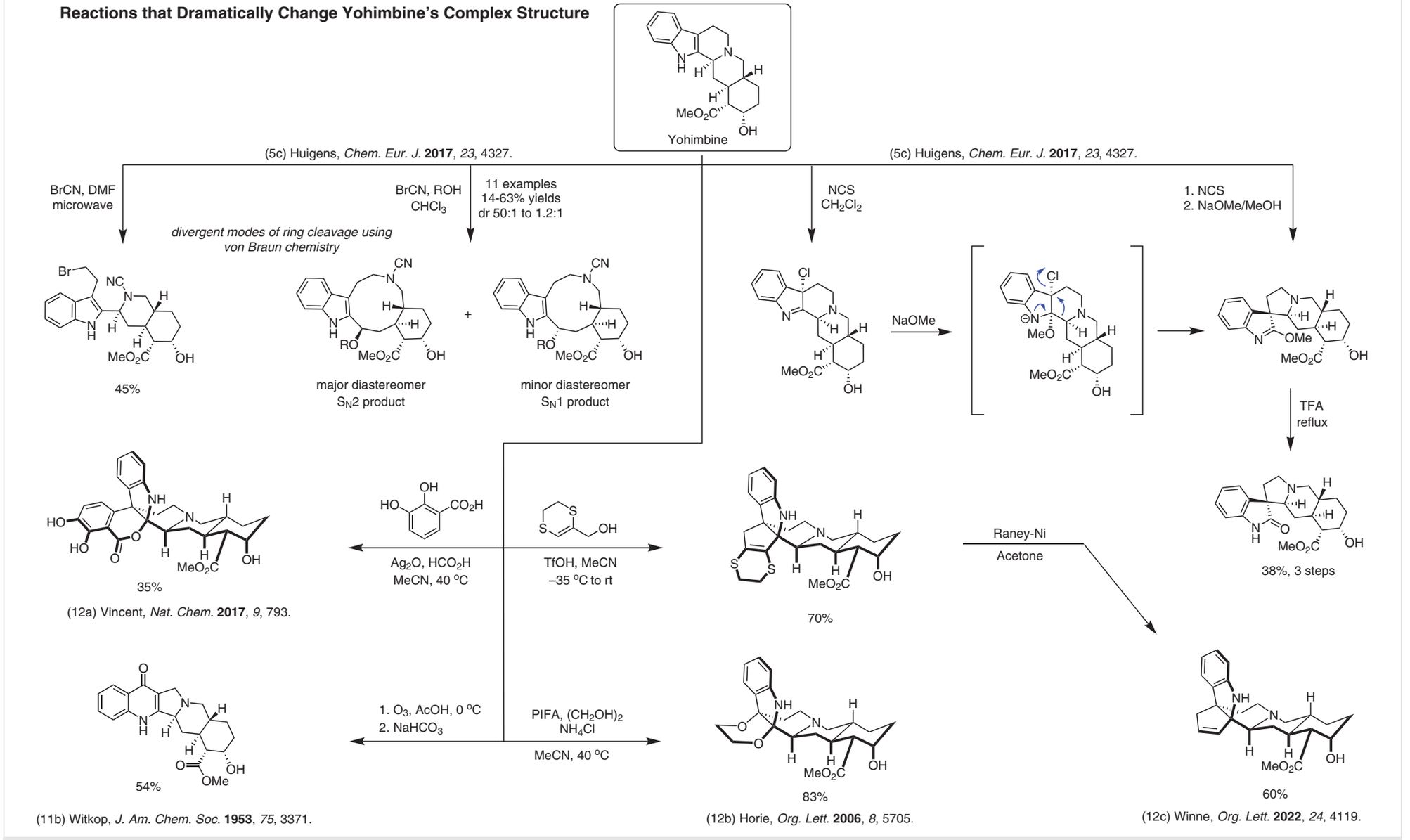


Figure 12 Reactions that dramatically change yohimbine's complex structure[5c,11b,12a–c]

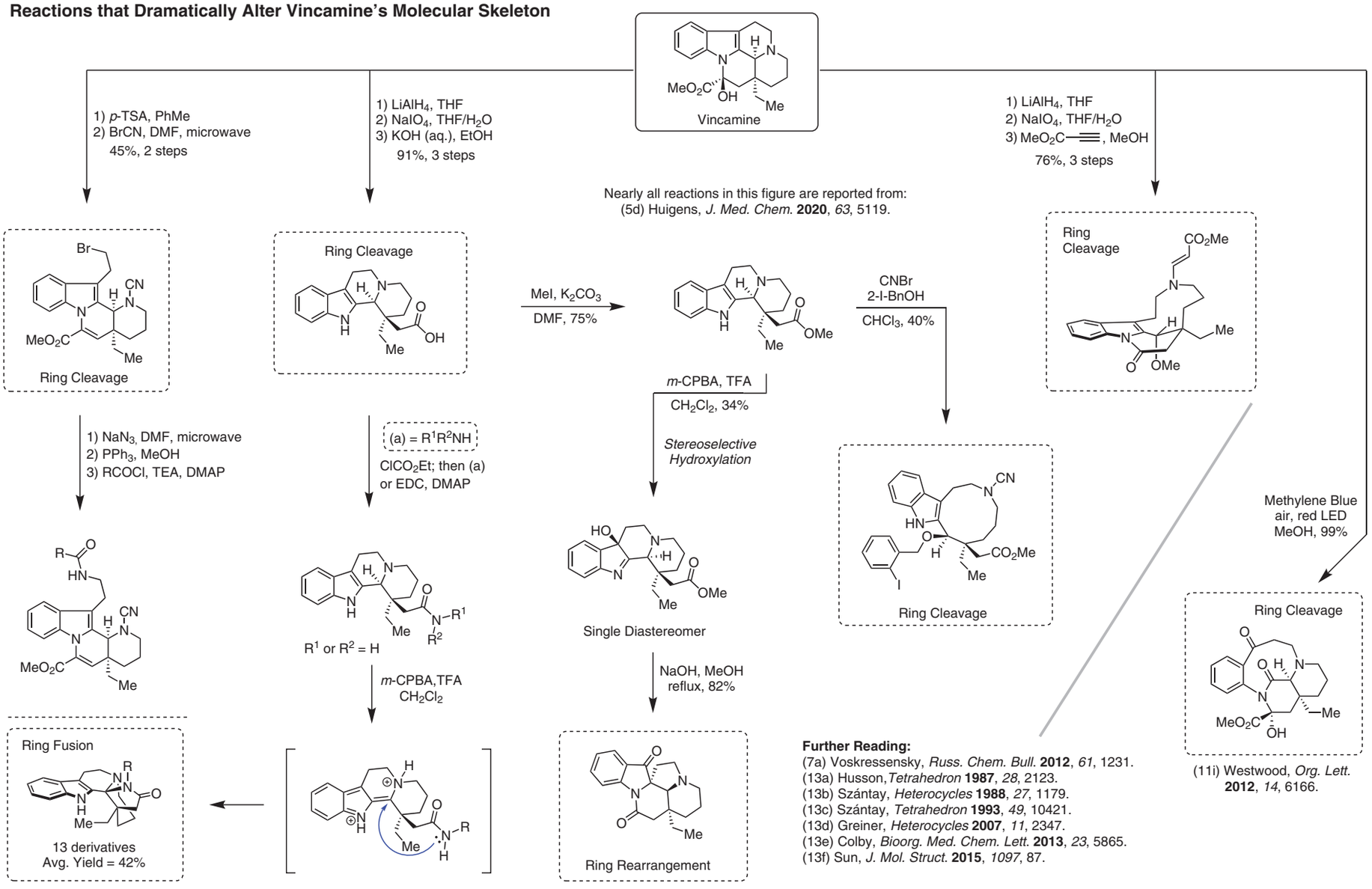


Figure 13 Reactions that dramatically alter vincamine's molecular skeleton[5d,7a,11i,13a–f]

Ring Distortion of the Indole Alkaloids Vincamine and Yohimbine: A Complexity-to-Diversity Approach to New Molecules for Drug Discovery

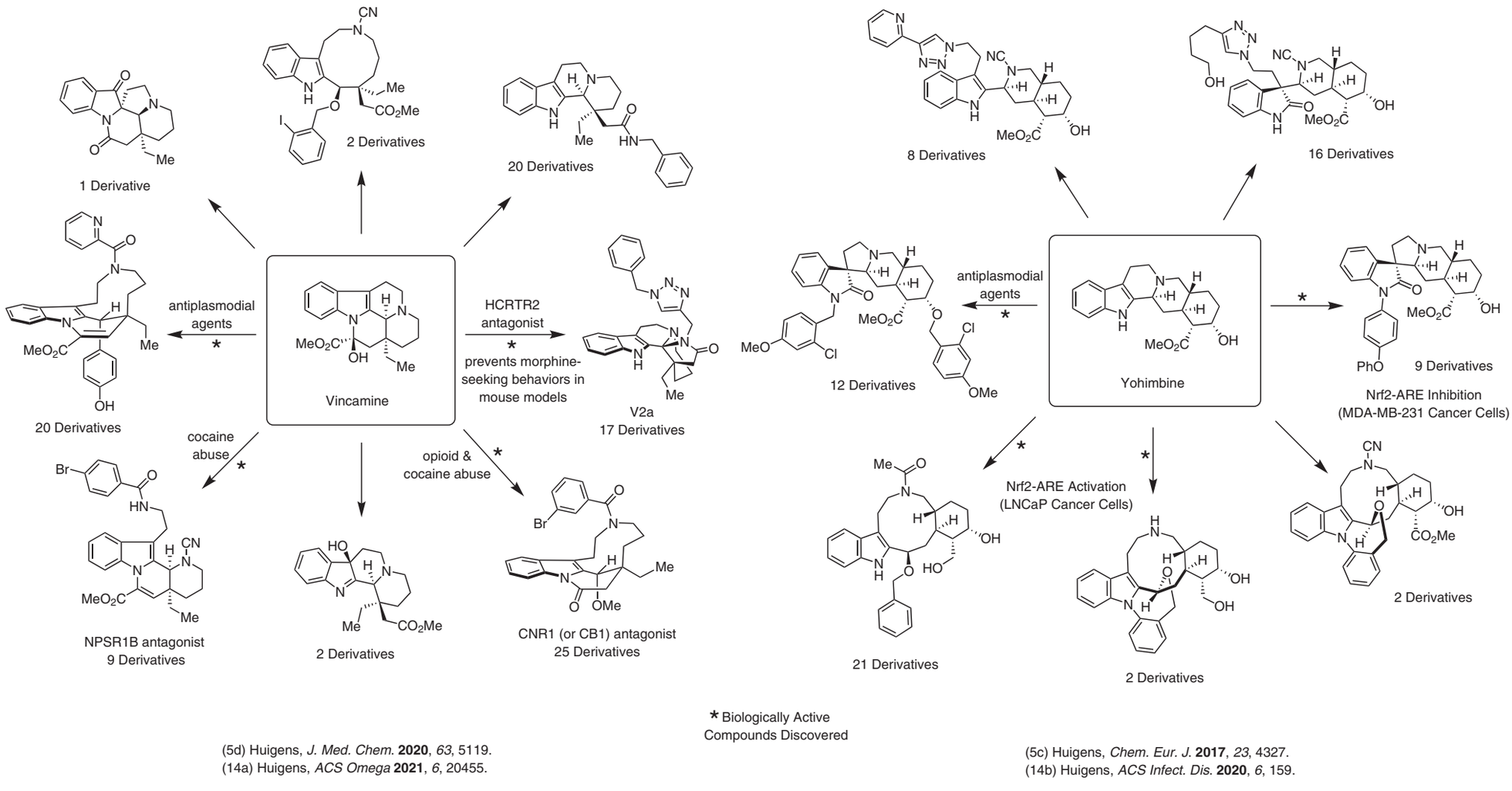


Figure 14 Ring distortion efforts of vincamine and yohimbine, and the discovery of biologically active small molecules in significant disease areas (e.g., cancer, opioid addiction, malaria)[5c,d,14a,b]

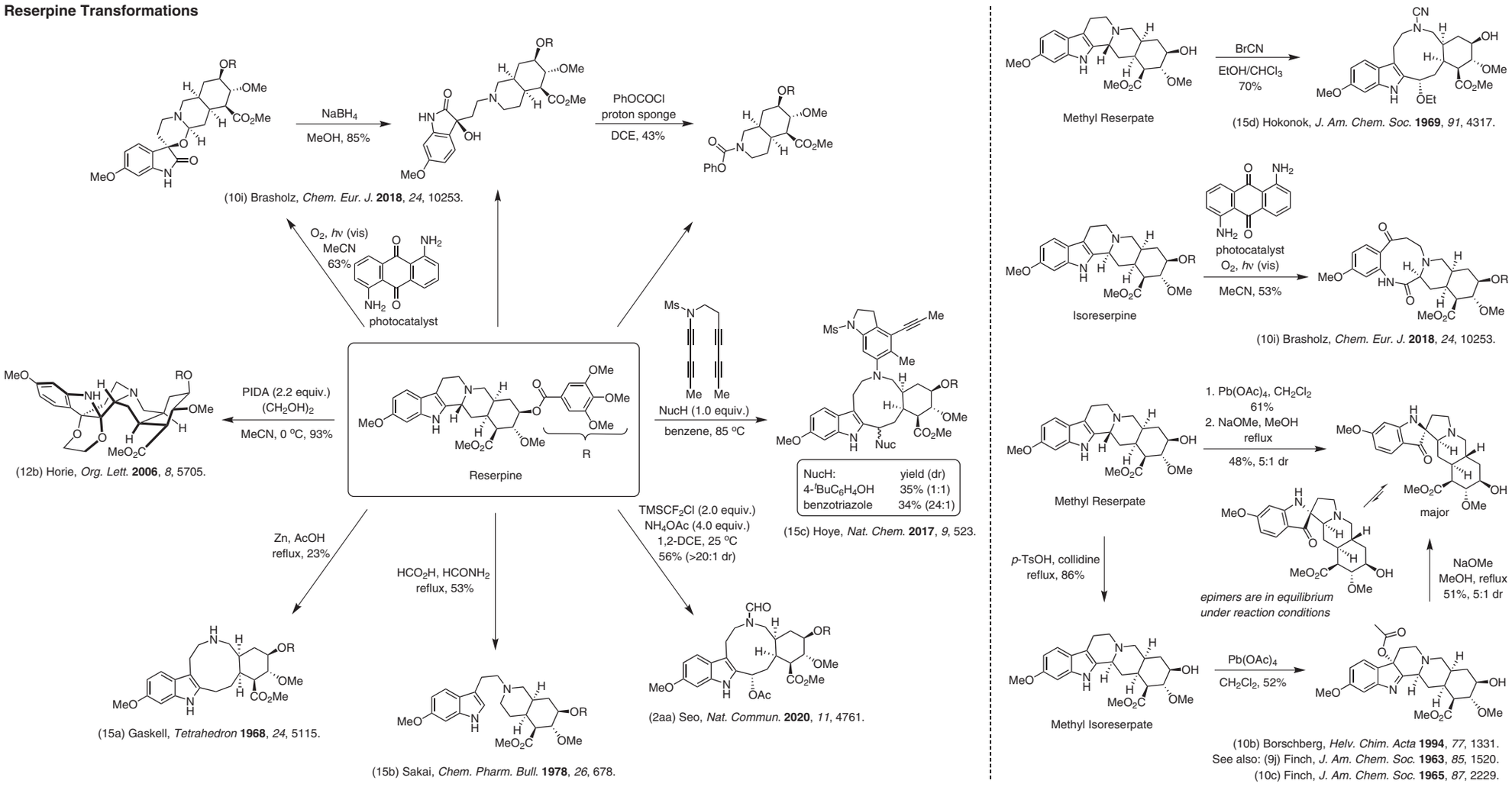


Figure 15 Chemical reactions of reserpine that significantly change its architecture[2aa,9j,10b,c,i,12b,15a–d]

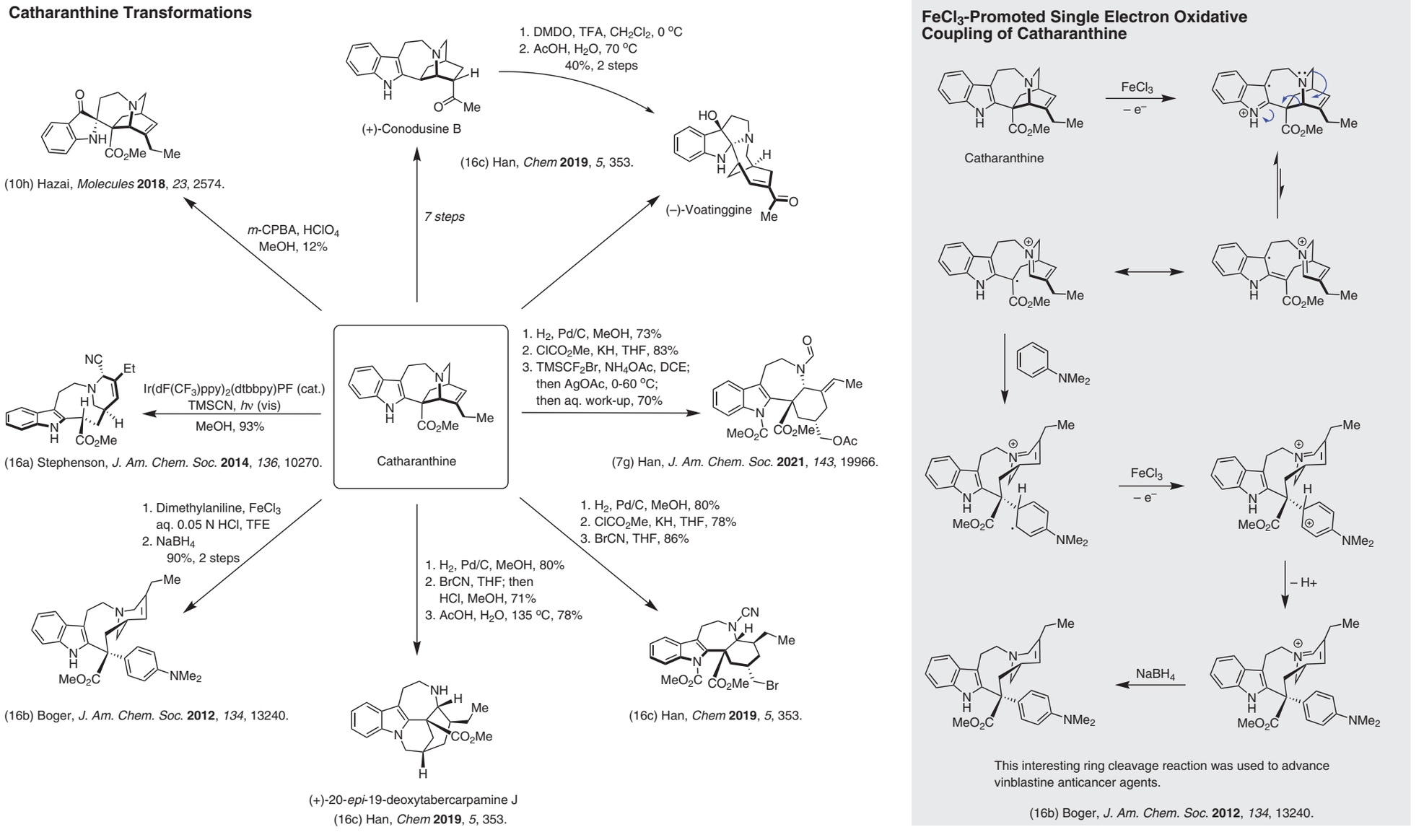
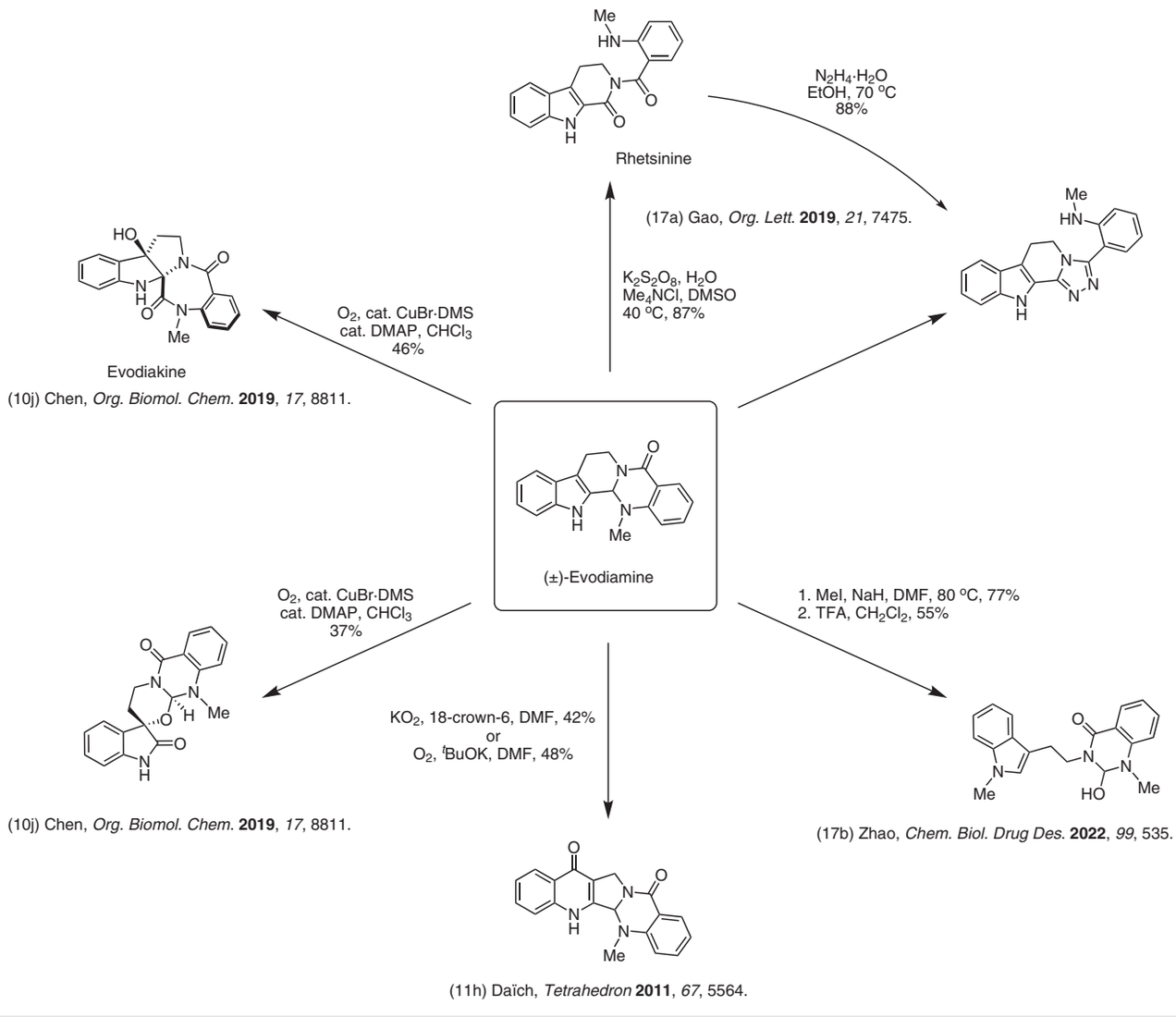
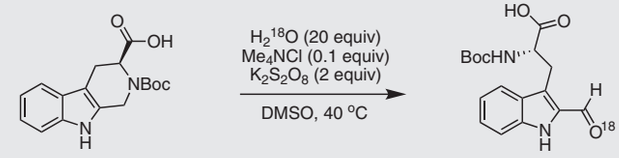


Figure 16 Reactions that alter catharanthine's complex structure[7g,10h,16a–c]

Evodiamine Transformations

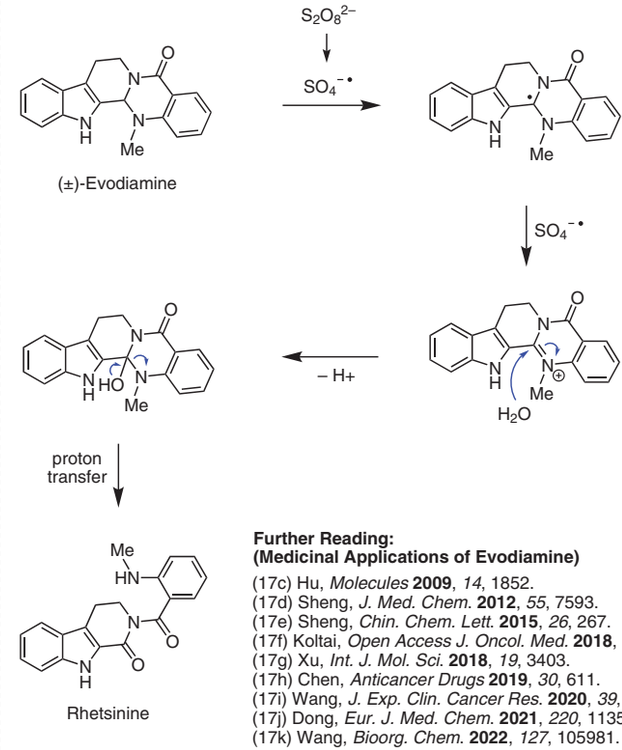


Oxidation of Tetrahydro-β-Carbolines by Persulfate



(17a) Gao, *Org. Lett.* **2019**, *21*, 7475. 25 examples, 52-90% yield

Proposed Mechanism for the Late-Stage Oxidation of Evodiamine



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(17k) Wang, *Bioorg. Chem.* **2022**, *127*, 105981.

Figure 17 Chemical reactions reported to dramatically change evodiamine's scaffold[10j,11h,17a–k]

Conflict of Interest

The authors declare no conflict of interest.

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