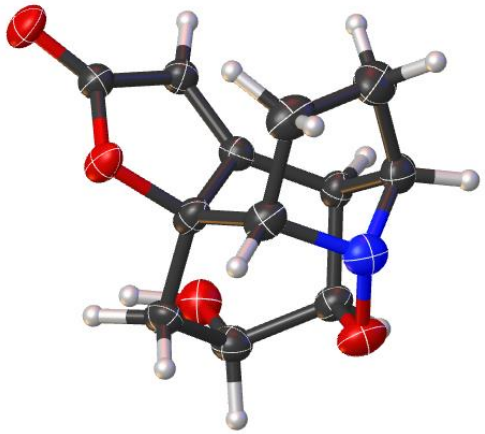
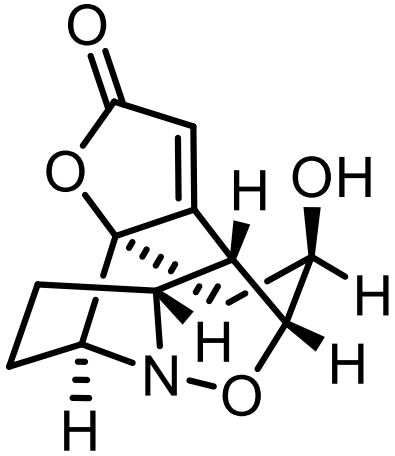
Total Synthesis of *Securinega* Alkaloids

Casey Olen
Denmark Group Meeting
January 31st, 2023





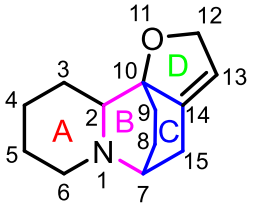
Overview

Part 1: Structural Features and Natural Occurrence of *Securinega* Alkaloids

- Four different types of “classical” (*i.e.* lower oxidation) monomers, non-classical oxidized monomers, and higher-order/oxidized oligomers
- Stereochemical considerations for epimeric and homologous alkaloids
- Structural determination and possible biosynthetic pathways

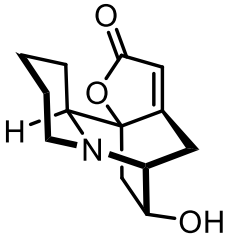
Part 2: Strategies for the Synthesis of Classical and Non-Classical Monomeric *Securinega* Alkaloids

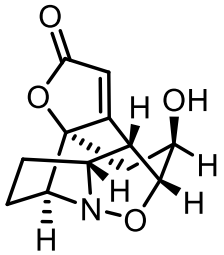
- Installation of the key C2-C9/10 bond
- Construction of azabicyclo[3.2.1]octane and azabicyclo[2.2.2]octane B/C ring systems
- Synthesis of menisdaurilide and (oxidized) monomeric alkaloids

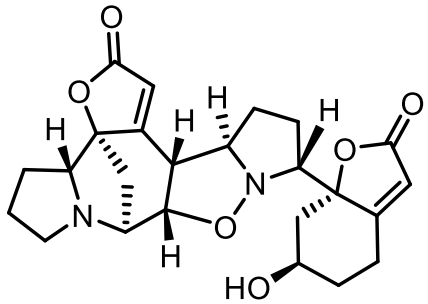


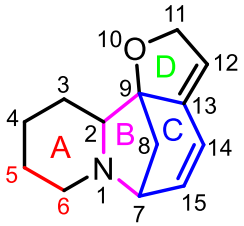
Part 3: Progress Towards the Synthesis of Higher Order Alkaloids

- Synthesis of flueggine A and flueggininе C





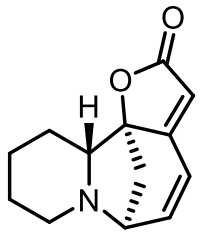




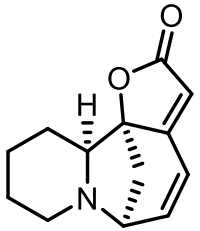
The Sea of *Securinega* Alkaloids

S. suffruticosa

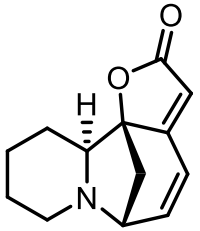
F. virosa



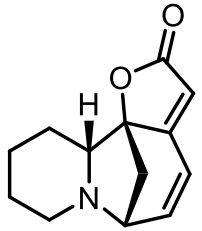
securinine (**1**)



allosecurinine (*2-epi*-**1**)



virosecurinine (*ent*-**1**)



viroallosecurinine (*ent*-*2-epi*-**1**)

- Securinine (**1**) was first isolated in 1956 and approved for medical use in USSR as a strychnine substitute.
- Occurs in species of subtropical shrubs in *Phyllanthaceae*. Rich sources include *Flueggea virosa* and *Securinega suffruticosa.*
- Modest neurological, antineoplastic, and antimicrobial effects with diverse mechanisms of action (bonus side effect: “heavy tetanic seizures”).
- More than 80 known alkaloids have been isolated. Unusual species-dependent distribution of stereoisomers in nature.
- One of the few classes of natural products that display naturally occurring enantiomeric members.

The Alkaloids, Vol. 74 (Ed.:H.-J.Knolker), Academic Press, London, **2015**, pp. 1–120. *Asian J. Org. Chem.* **2017**, 6, 1146–1159.

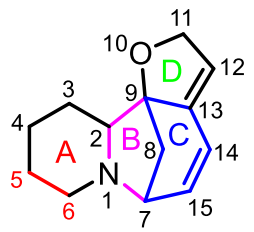
The Sea of *Securinega* Alkaloids

Four structural types of simple monomeric Securinega alkaloids:

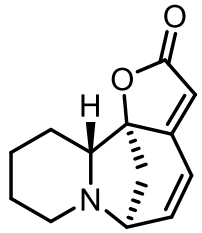
Azabicyclo[3.2.1]octane B/C ring system

Azabicyclo[2.2.2]octane B/C ring system

Class I

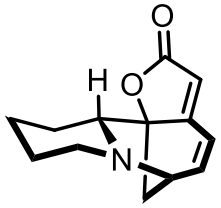


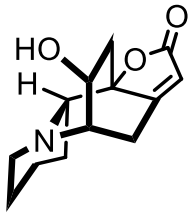
securinane core



securinine (**1**)

≡





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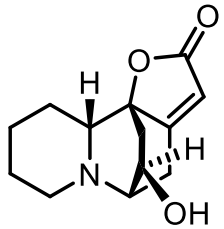
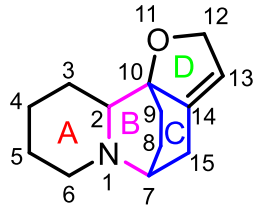


securinol A



neosecurinane core

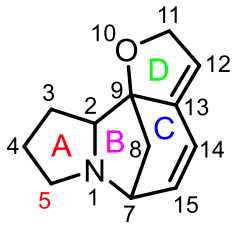
Class III

A ring dehomologation

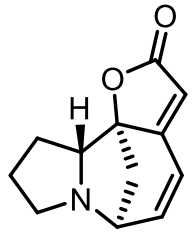
Note that in C6 is omitted for norsecurinane-type cores

A ring dehomologation

Class II

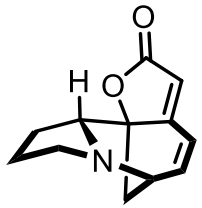


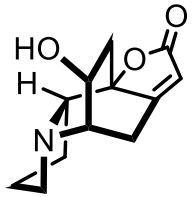
norsecurinane core



norsecurinine

≡





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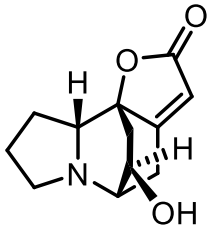
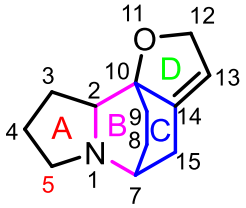


bubbialine

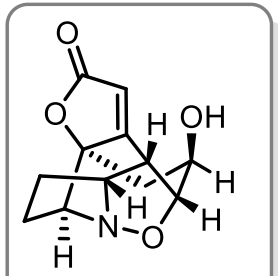


neonorsecurinane core

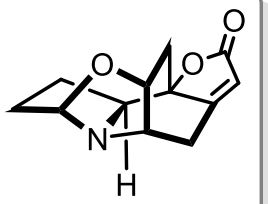
Class IV

The Sea of *Securinega* Alkaloids

There are several examples of deviations from these 4 base structures:

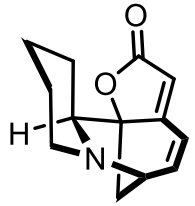


virosaine A



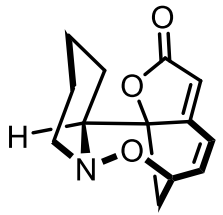
niurine

Can be made directly from classical alkaloids by oxidation in some cases:



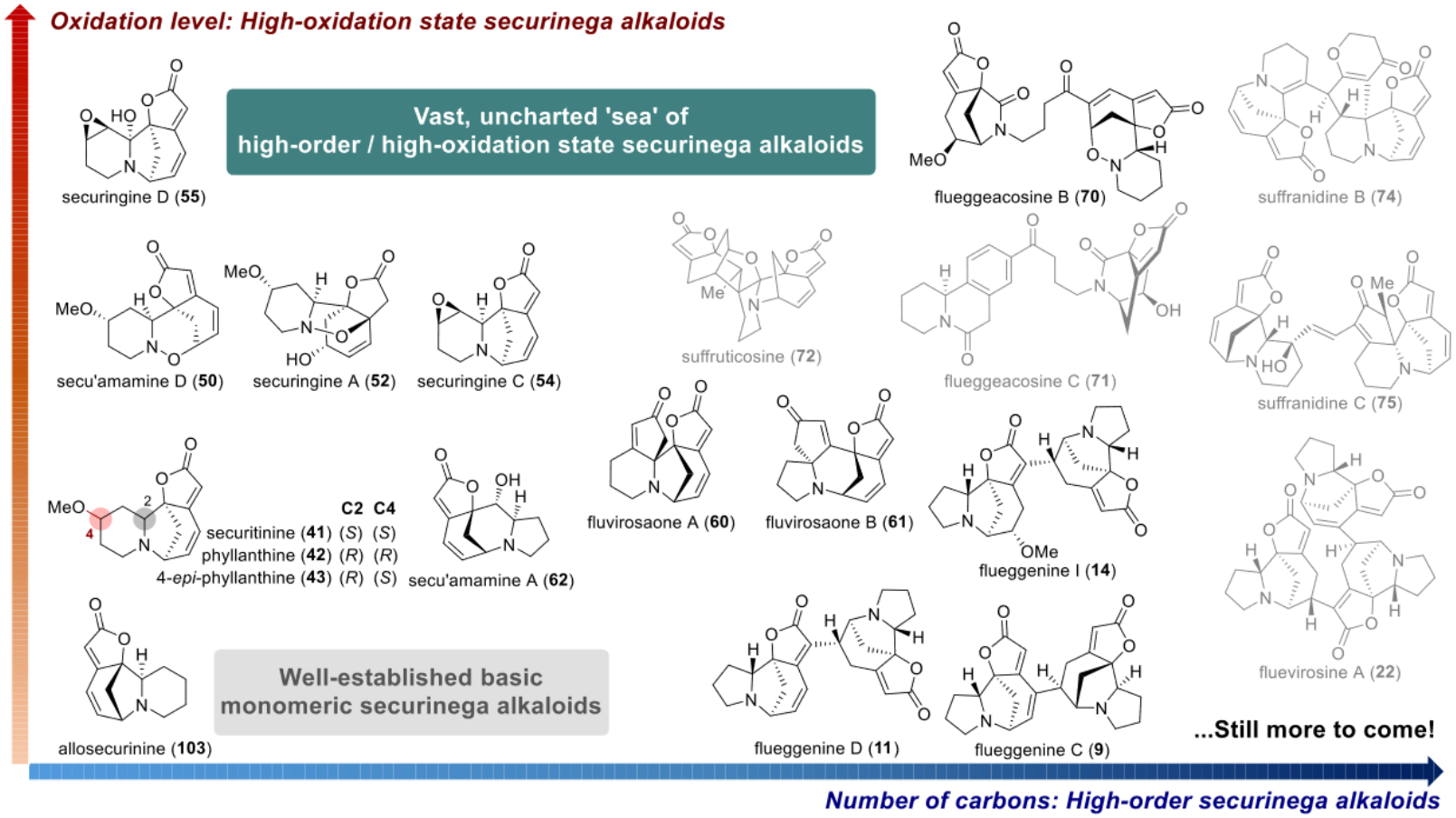
allosecurinine

H_2O_2 →



phyllantidine

Starting in 2006, a variety of higher-order oligomeric alkaloids have been discovered, all from *F. virosa* with incorporation of up to 5 monomers:



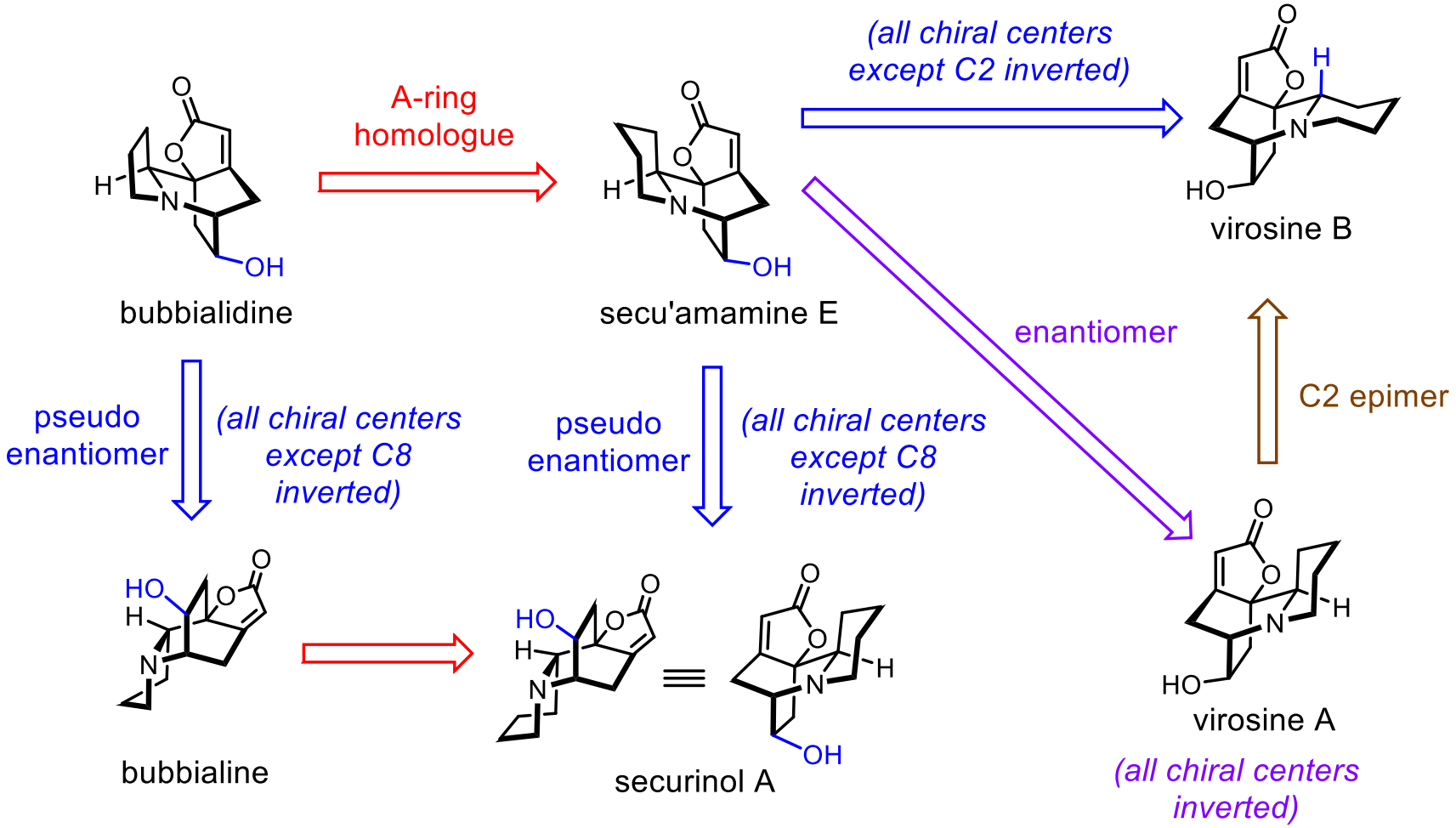
Asian J. Org. Chem. **2017**, 6, 1146–1159. *Org. Lett.* **2006**, 8, 2285–2288. *Acc. Chem. Res.* **2023**, 56, 140−156.

Enantio- and Pseudoenantio-morphism

<u>*Securinega* alkaloid stereochemistry is complicated and naming can be confusing:</u>

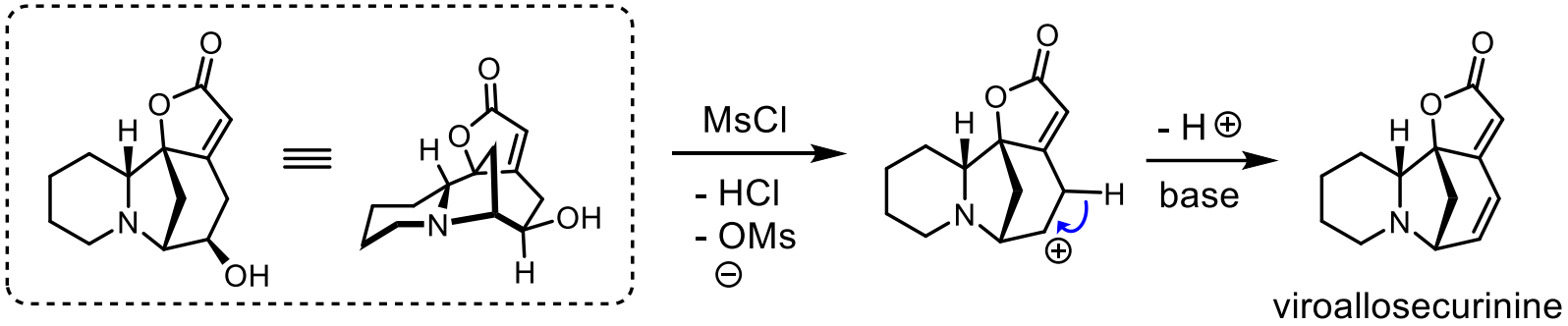
Historically, degradation studies were used to assign connectivity. Today, connectivity is determined through 2D NMR.

If XRD is not possible, CD comparisons are used to determine morphology – this has led to erroneous and conflicting assignments in the literature.



Structural Determination: Securinol A Case Study

Original structure proposed for securinol A (Horii, 1965):

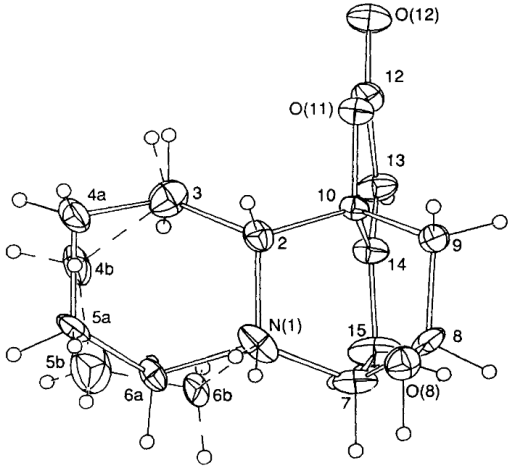


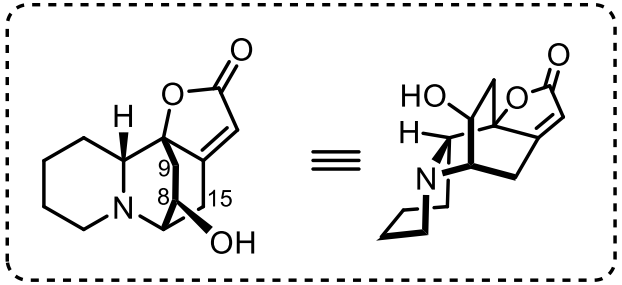
securinol A?

This structure was supported by degradation studies.

A later detailed 2D NMR analysis supported this assignment (Beutner, 1987).

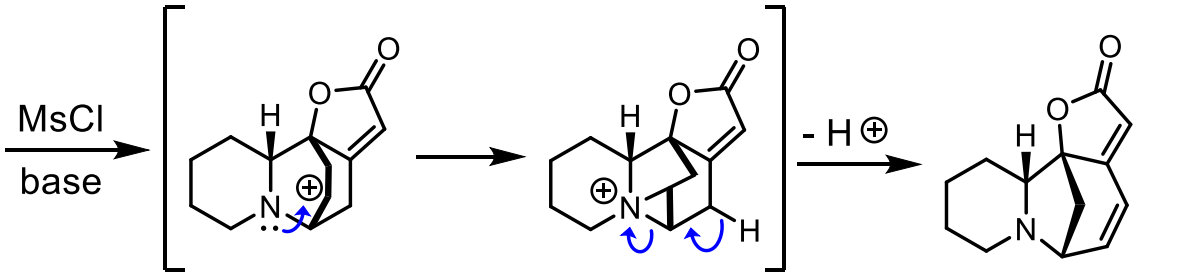
The proposal was later shown to be incorrect by XRD (White, 1991):





securinol A

The source of confusion:



viroallosecurinine

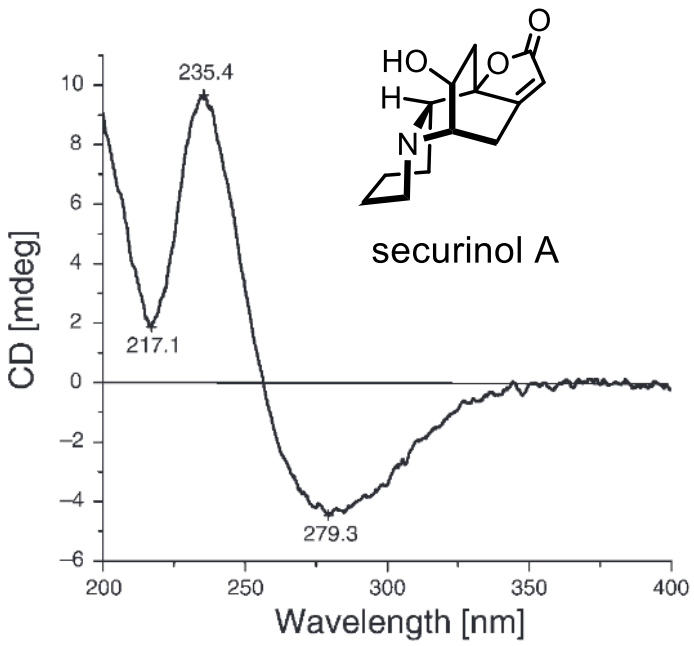
Chem. Pharm. Bull. Jpn. **1965**, 13, 1307. *Tetrahedron* **1987,** 43, 13, 2915 - 2924. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1863 - 1869.

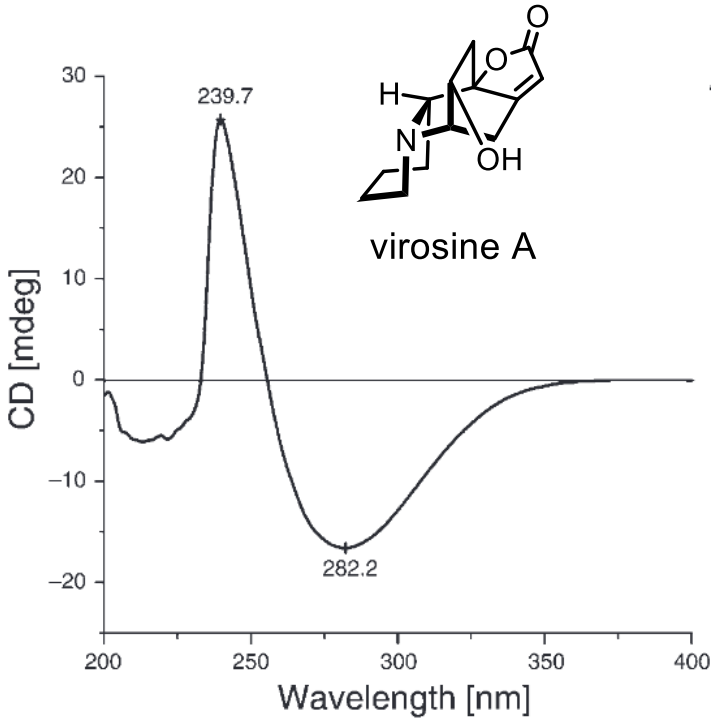
Structural Determination: Securinol A Case Study

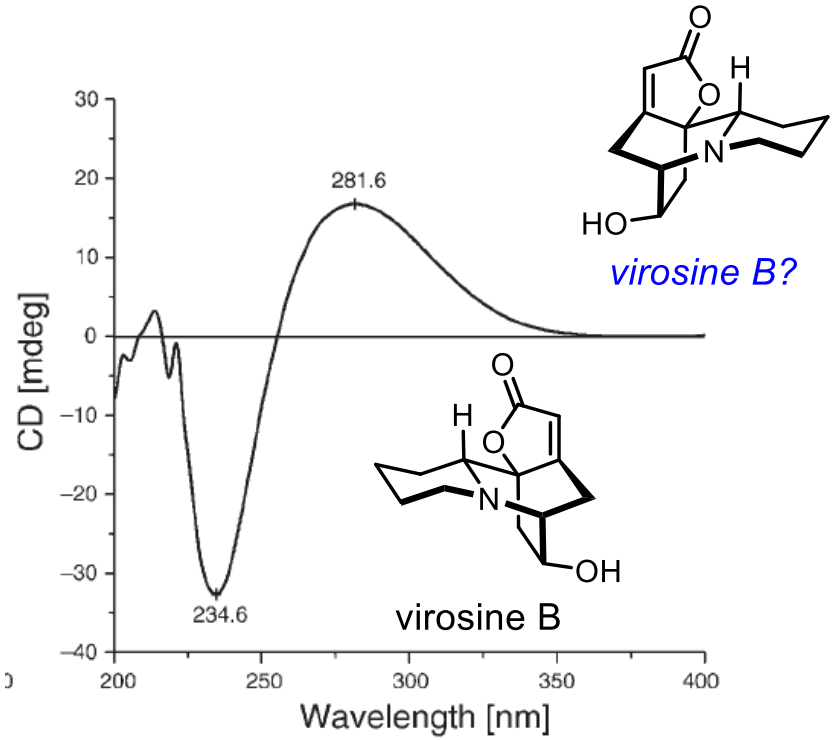
Virosines A and B configurations assigned based on CD comparison to securinol A (Ye, 2008):

Opposite Cotton effect observed for virosine B originally attributed to inverted configurations at C7 and C10.

Recent total synthesis of virosine B suggests that the correct structure is the enantiomer of the original proposal (Quideau, 2019):



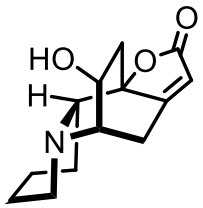




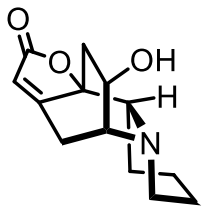
Chem. Eur.J. **2019**, *25, 11574 - 11580. Helv. Chim. Acta.* **2008**, *91, 1124.*

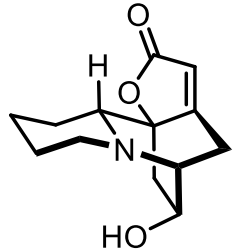
Further complications: a meticulous recent separation of *F. virosa* extract by chiral HPLC revealed that all 8 stereoisomers of securinol A occur in the plant (Zhang, 2017):

To date, *F. virosa* is ***the only organism known to produce all possible stereoisomers of a natural product with >2 stereogenic centers.***

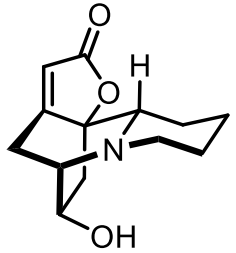


securinol A

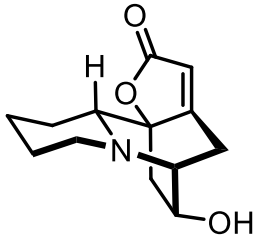




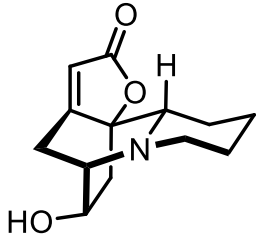
2-episecurinol A?



2-episecurinol A

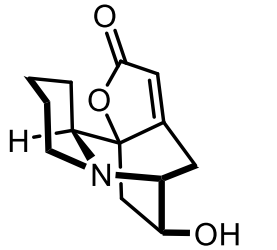


virosine B

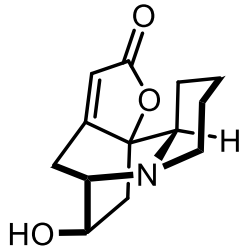


virosine B?

Tetrahedron **2017**, 73, 4692 – 4697.



secu'amamine E



virosine A

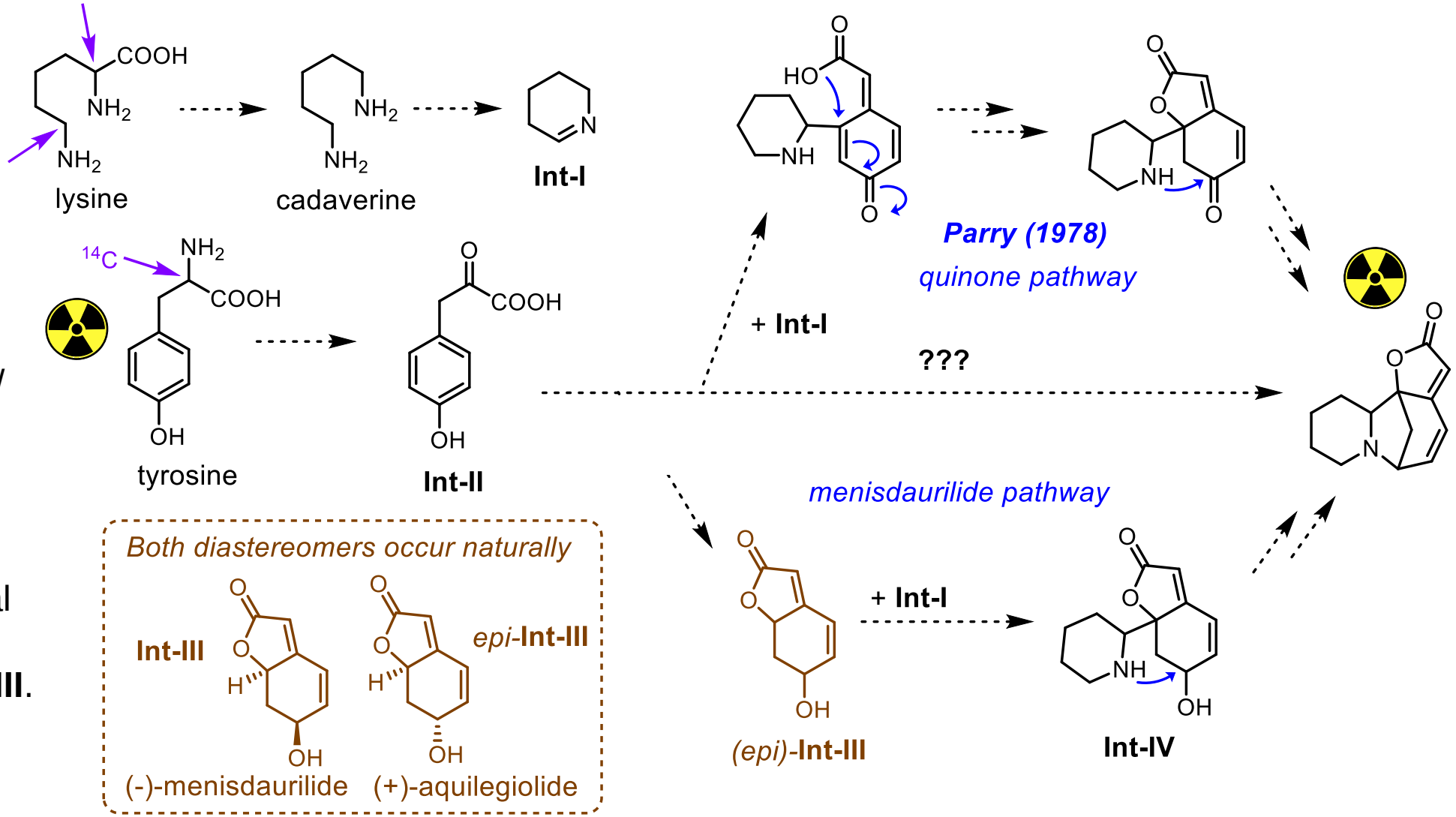
Chem. Eur.J. **2019**, *25, 11574 - 11580. Helv. Chim. Acta.* **2008**, *91, 1124.*

Biosynthesis of *Securinega* Alkaloids

^{14}C radiolabelling studies confirm **1** is derived from lysine and tyrosine, proceeding through putative **Int-I** and **Int-II**.

The order of **Int-I** addition/ **Int-II** dearomatization is contentious.

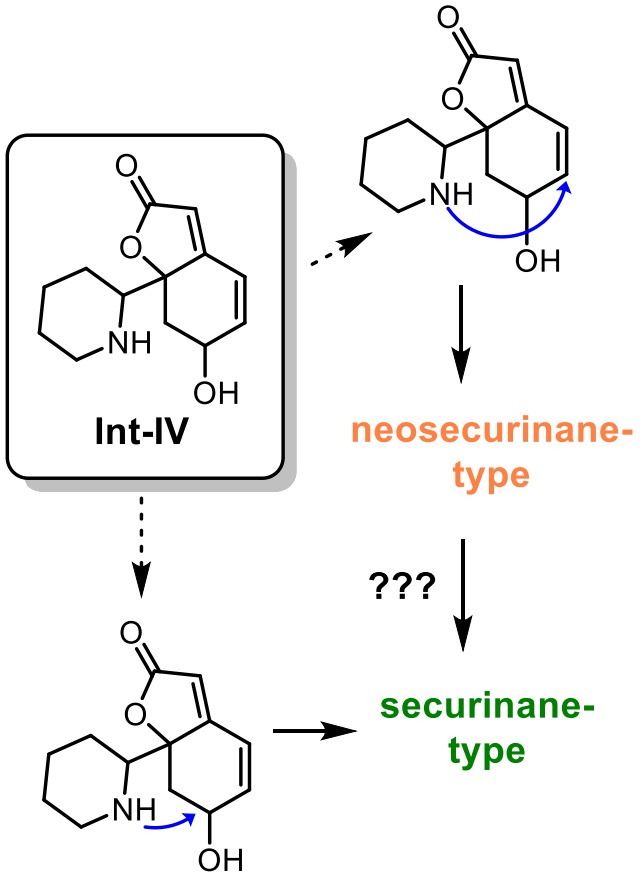
2008 revised biosynthesis is supported by the natural occurrence of epimeric possible intermediate **Int-III**.



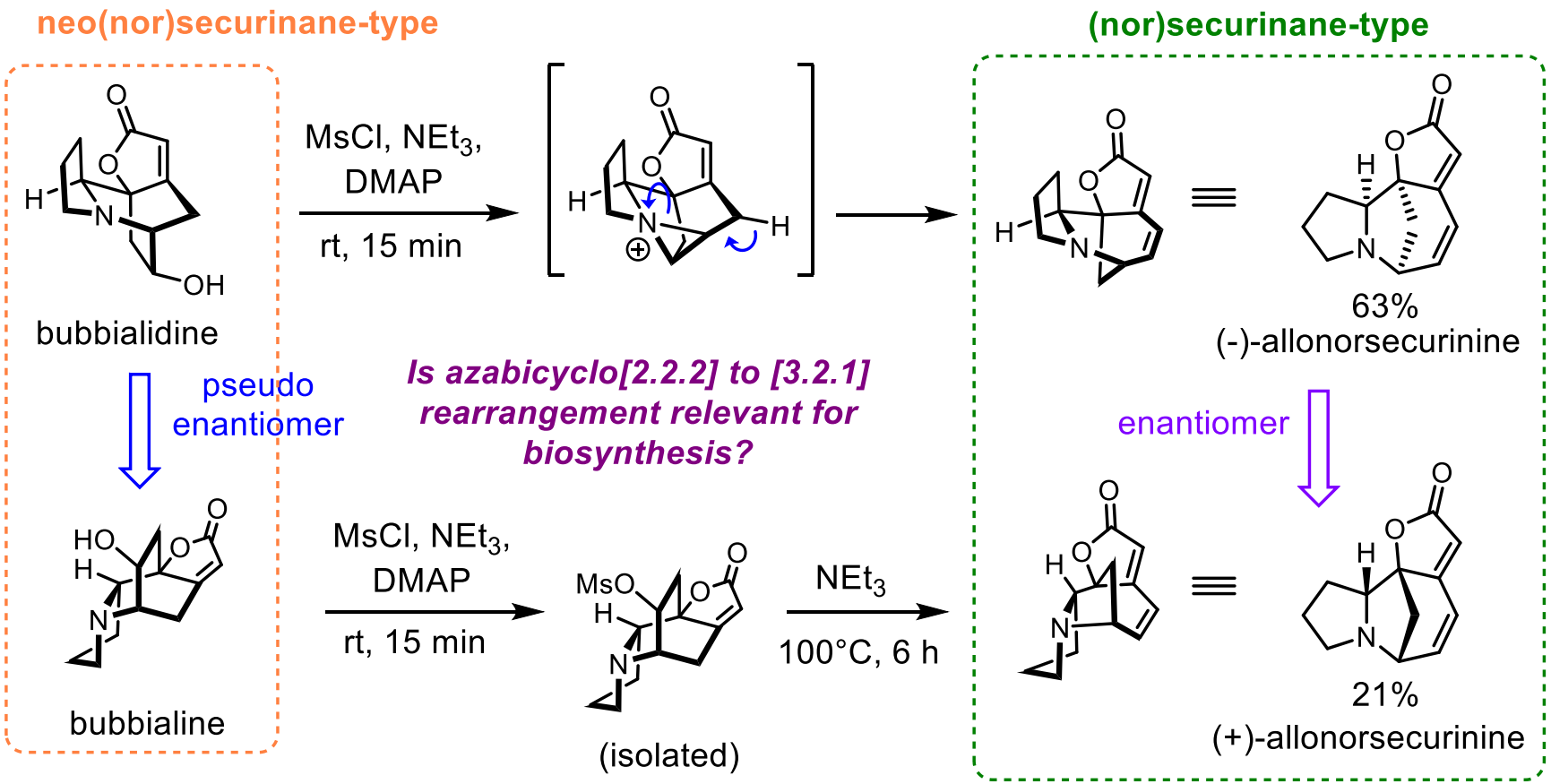
Chem. Eur. J. **2019**, 25,11574-11580. *J. Org. Chem.* **2008,** 73, 7657-7662. *Bioorg. Chem.* **1978**, 7, 277-288.

Biosynthesis of *Securinega* Alkaloids

Exact path of **Int-IV** to the final products is also unclear:



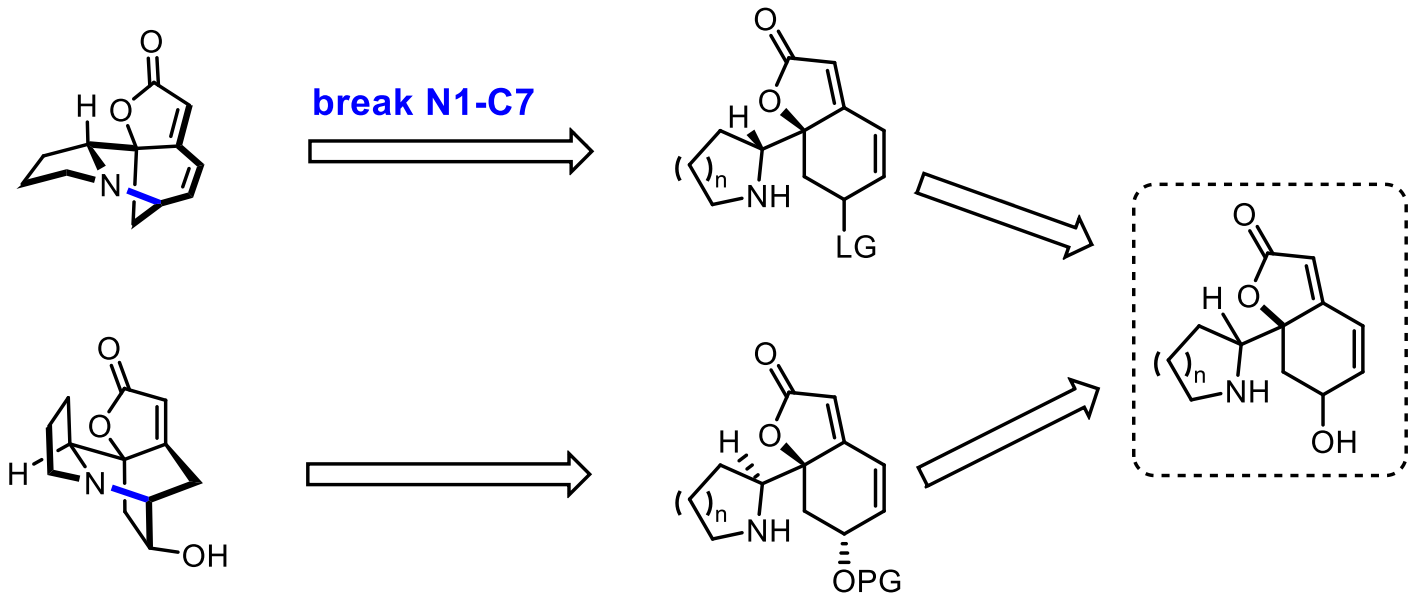
Plausible biosynthetic hypothesis invokes the direct production of enantiomeric (nor)securinane-type alkaloids from (pseudo)enantiomeric neo(nor)securinane-types (Gademann, 2017):



Org. Lett. **2017**, 19, 548−551. *Asian J. Org. Chem.* **2017**, 6, 1146–1159.

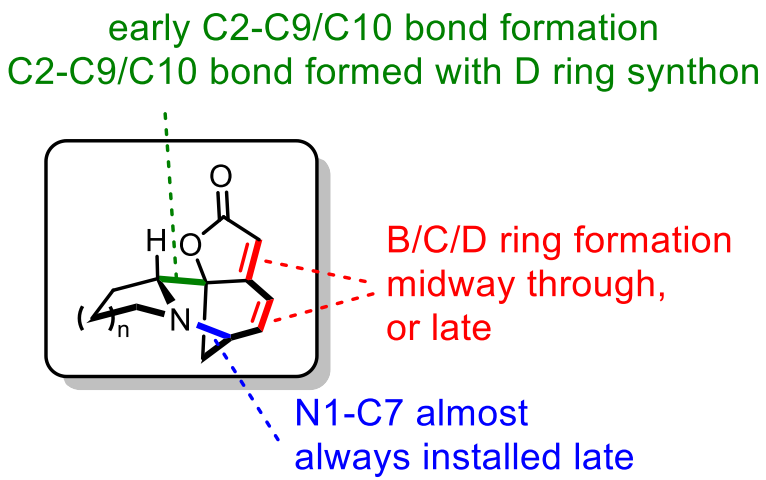
General Retrosynthetic Analysis for Monomeric Alkaloids

Monomeric alkaloids can be accessed from a common intermediate:



n = 1; norsecurinane-type (III/IV)
n = 2; securinane-type (I/II)

The key is setting the stereochemistry of the C2-C9/10 bond

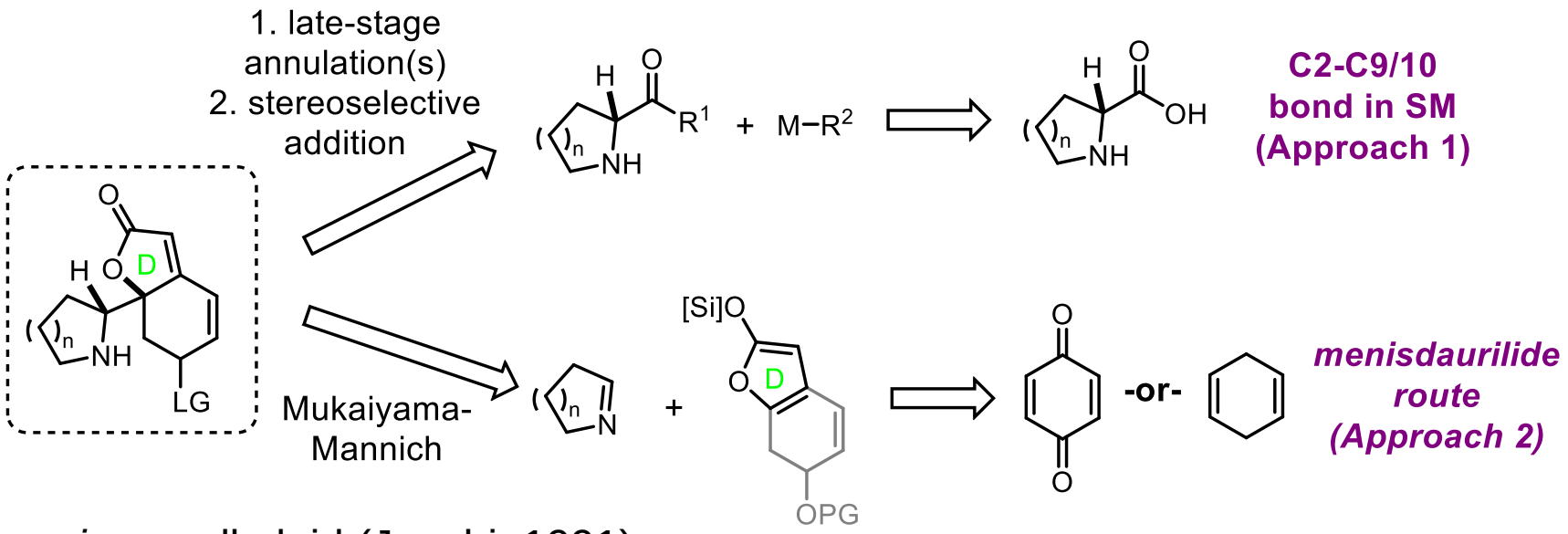


We can broadly divide synthetic approaches based on when the C2-C9/10 bond is formed.

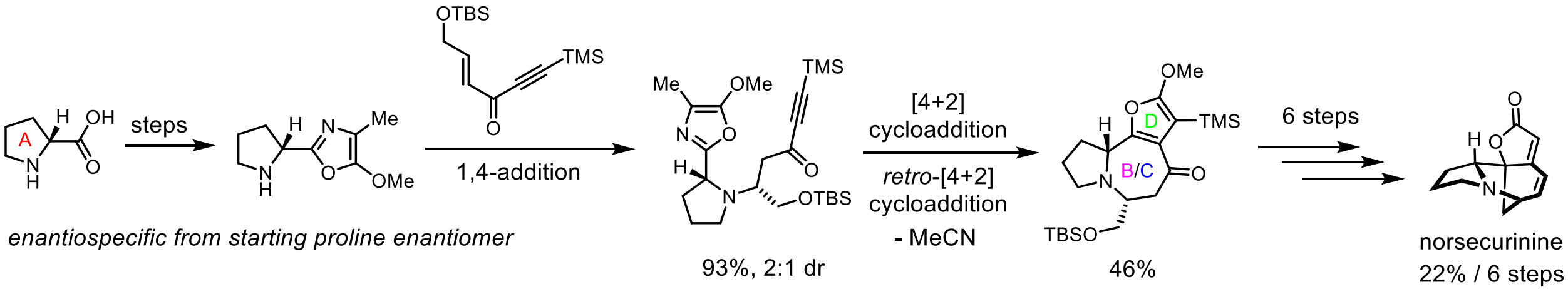
Strategies for Forming the C2-C9/10 Bond

Two main approaches:

1. C2-C9/10 bond with set C2 configuration, then intramolecular closure of B/C rings.
2. Installation of C2-C9/10 using D-ring as a vinylogous Mukaiyama-Mannich synthon.



First enantiospecific synthesis of a *Securinega* alkaloid (Jacobi, 1991):



enantiospecific from starting proline enantiomer

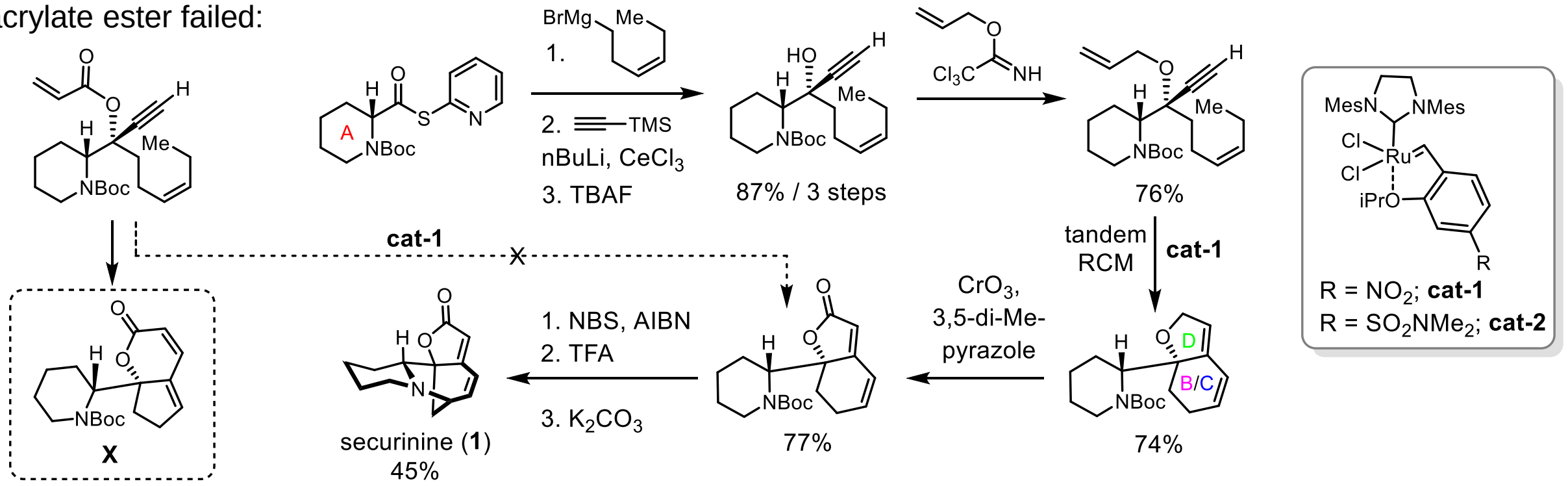
J. Am. Chem. Soc. **1991**, 113, 5384-5392.

Tandem RCM Ring Closure Controlled by C2 Configuration

A-ring installation via Approach 1 often precedes tandem RCM steps to close B/C/D rings.

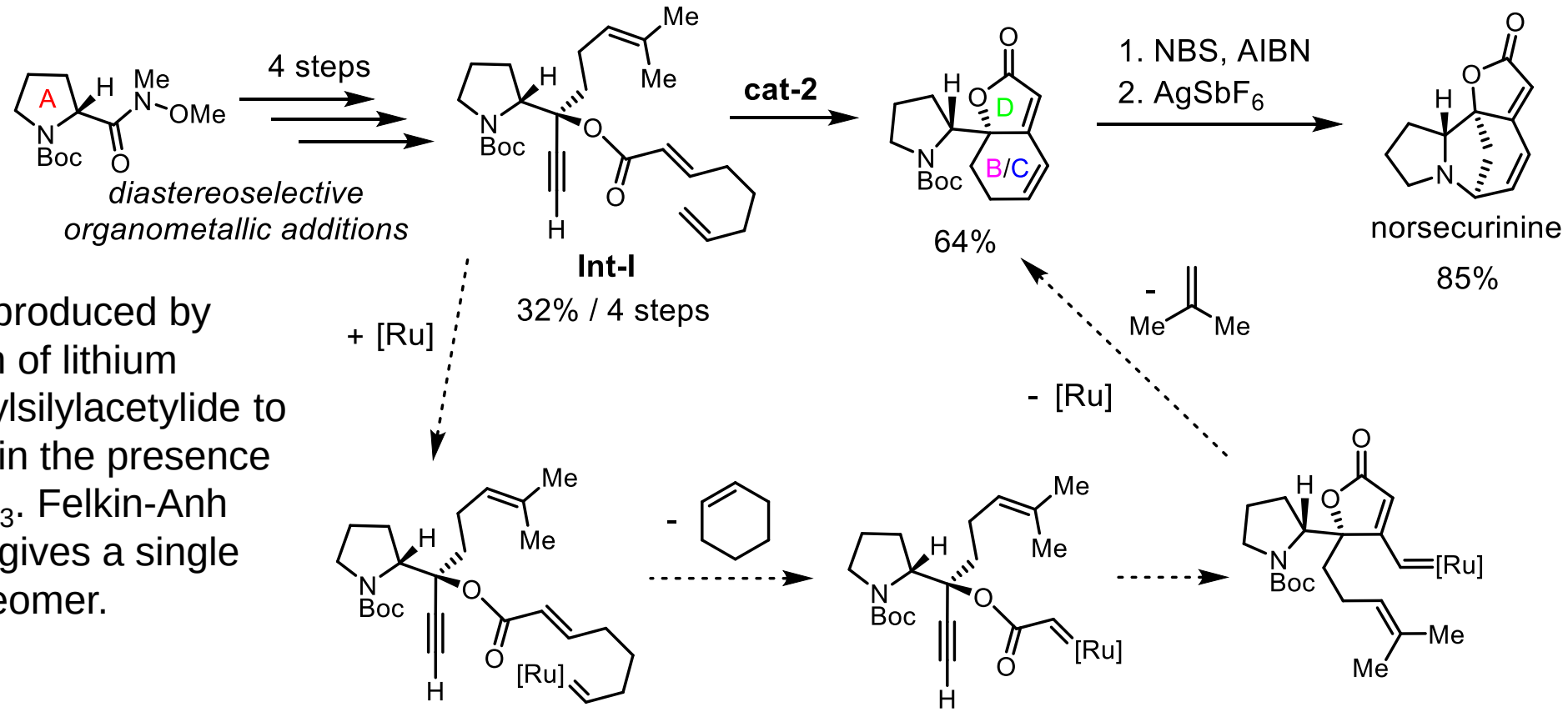
<u>First stereoselective synthesis of **1,** Approach 1 followed by tandem RCM (Honda, 2004):</u>

Tandem RCM from acrylate ester failed:

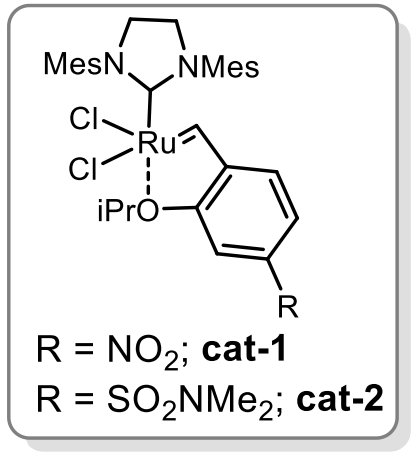


Tandem RCM Ring Closure Controlled by C2 Configuration

Efficient synthesis of norsecurinine by tandem RCM relay catalysis (Yang, Li, 2013):



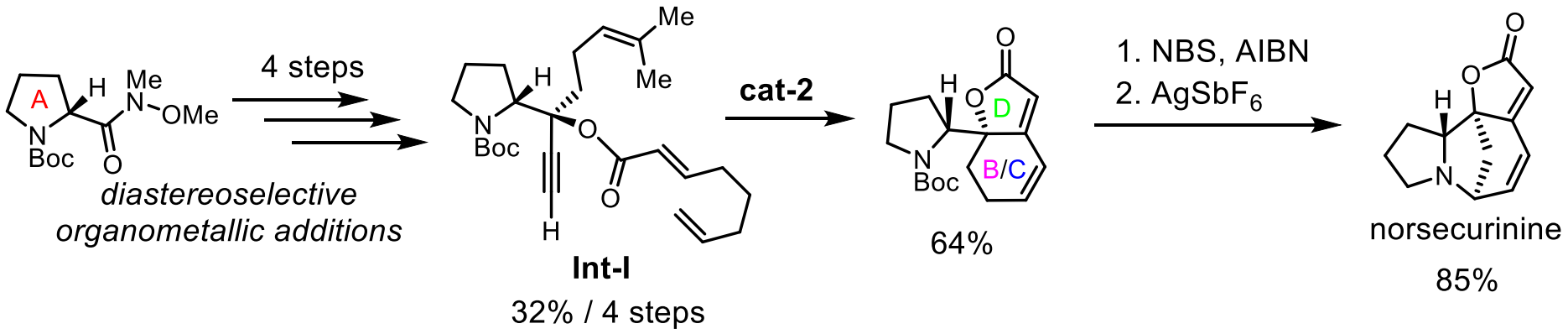
Int-I is produced by addition of lithium trimethylsilylacetylide to ketone in the presence of $CeCl_3$. Felkin-Anh control gives a single diastereomer.

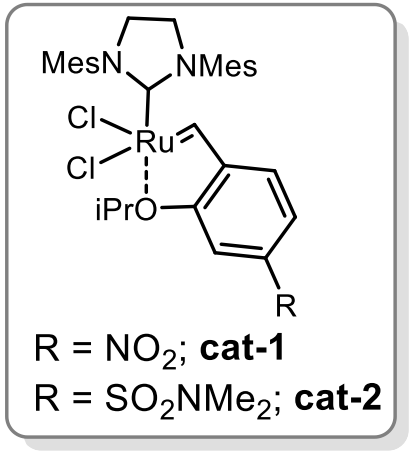


Org. Lett. **2004**, 6, 1, 87-89. *Angew. Chem.* **2013** 125, 2, 648–652. https://doi.org/10.1002/ange.201208261.

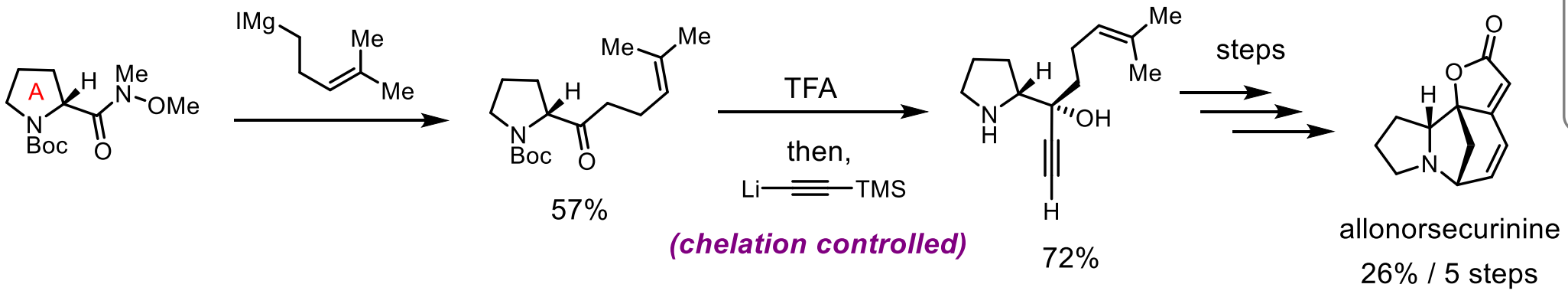
Tandem RCM Ring Closure Controlled by C2 Configuration

Efficient synthesis of norsecurinine by tandem RCM relay catalysis (Yang, Li, 2013):





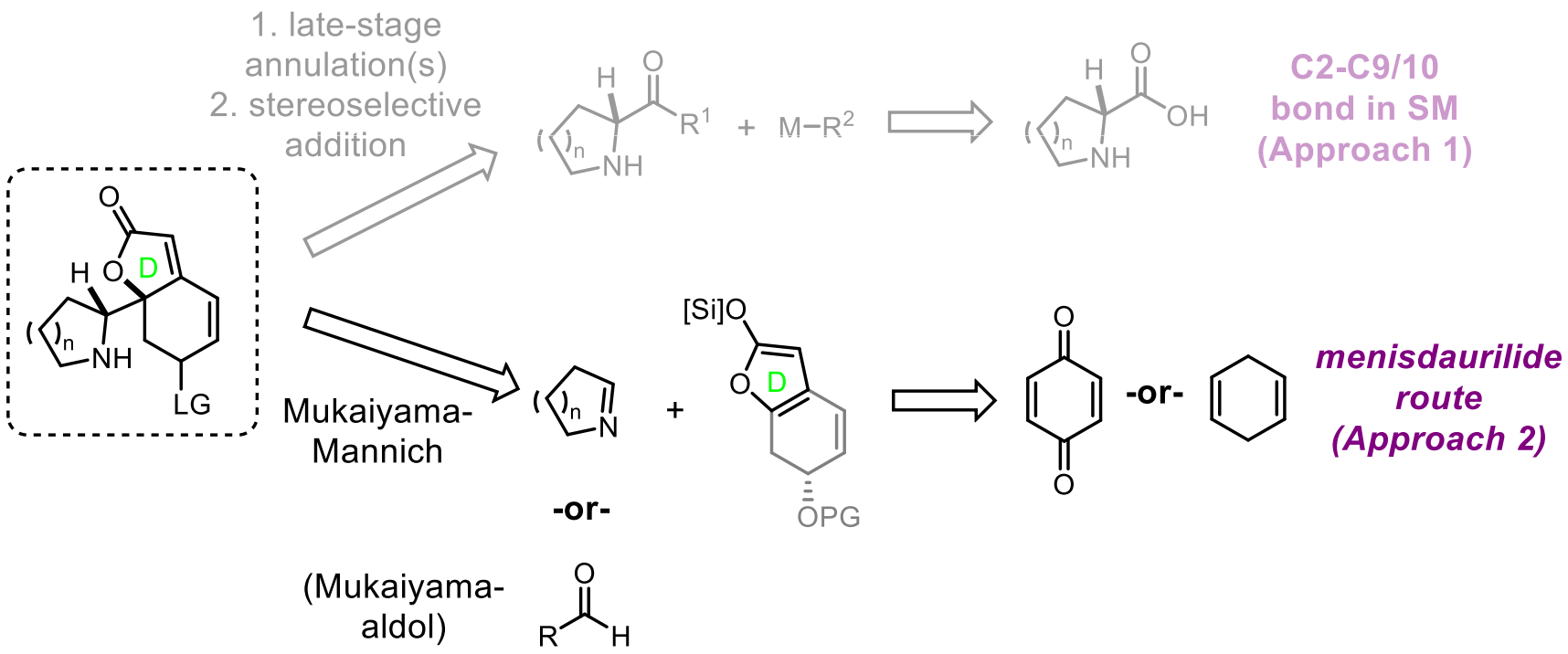
Other diastereomer via a chelation-controlled addition, elaborated to allonorsecurinine:



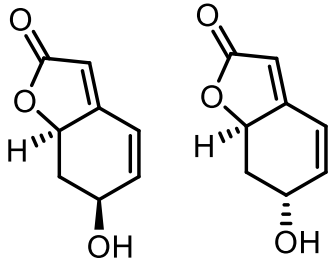
Menisdaurilide Route for Forming C2-C9/10 Bond

Two main approaches:

1. C2-C9/10 bond with set C2 configuration, then intramolecular closure of B/C rings.
2. Installation of C2-C9/10 using D-ring as a vinylogous Mukaiyama-Mannich synthon.



Both diastereomers occur naturally

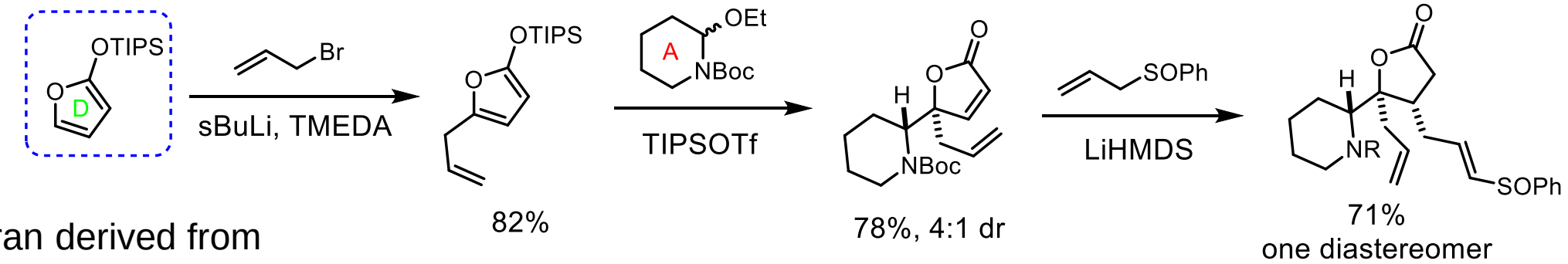


(-)-menisdaurilide (+)-aquilegiolide

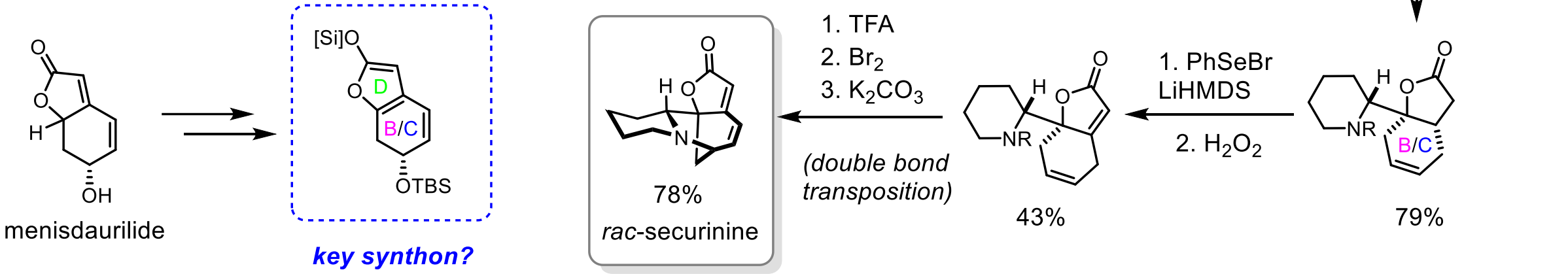
The key to this approach is realizing diastereoselective additions of a D-ring siloxyfuran synthon.

Pioneering Work Towards Menisdaurilide Route

Classic synthesis demonstrated the feasibility of installing C2-C9 bond by Mukaiyama-Mannich reaction (Lira, 2001):



Could a siloxyfuran derived from menisdaurilide or aquilegiolide engage in similar reactivity?

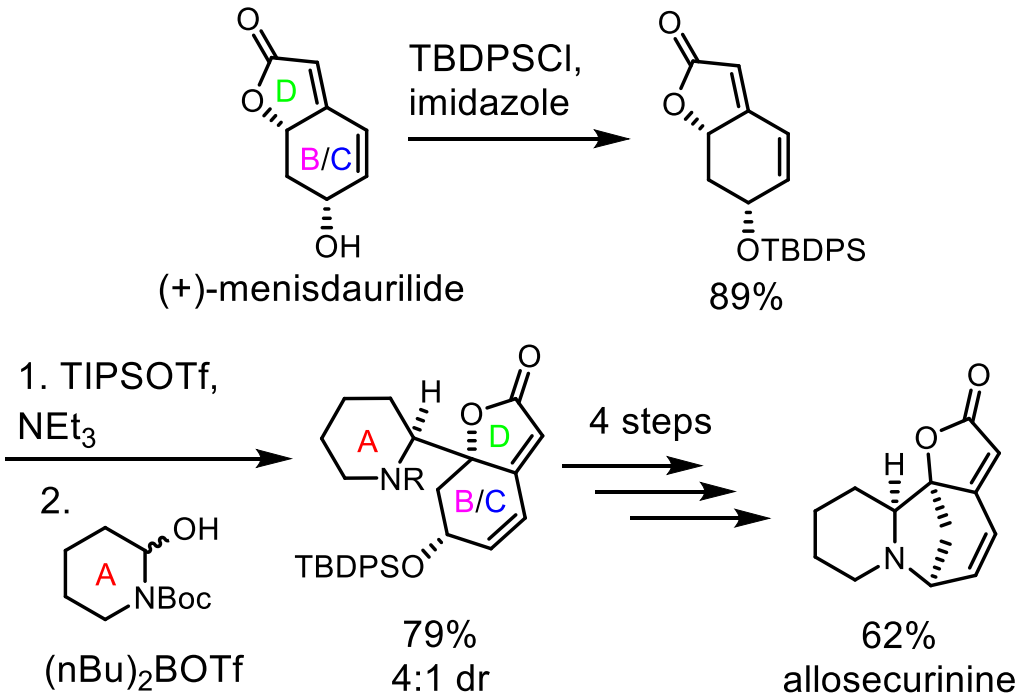


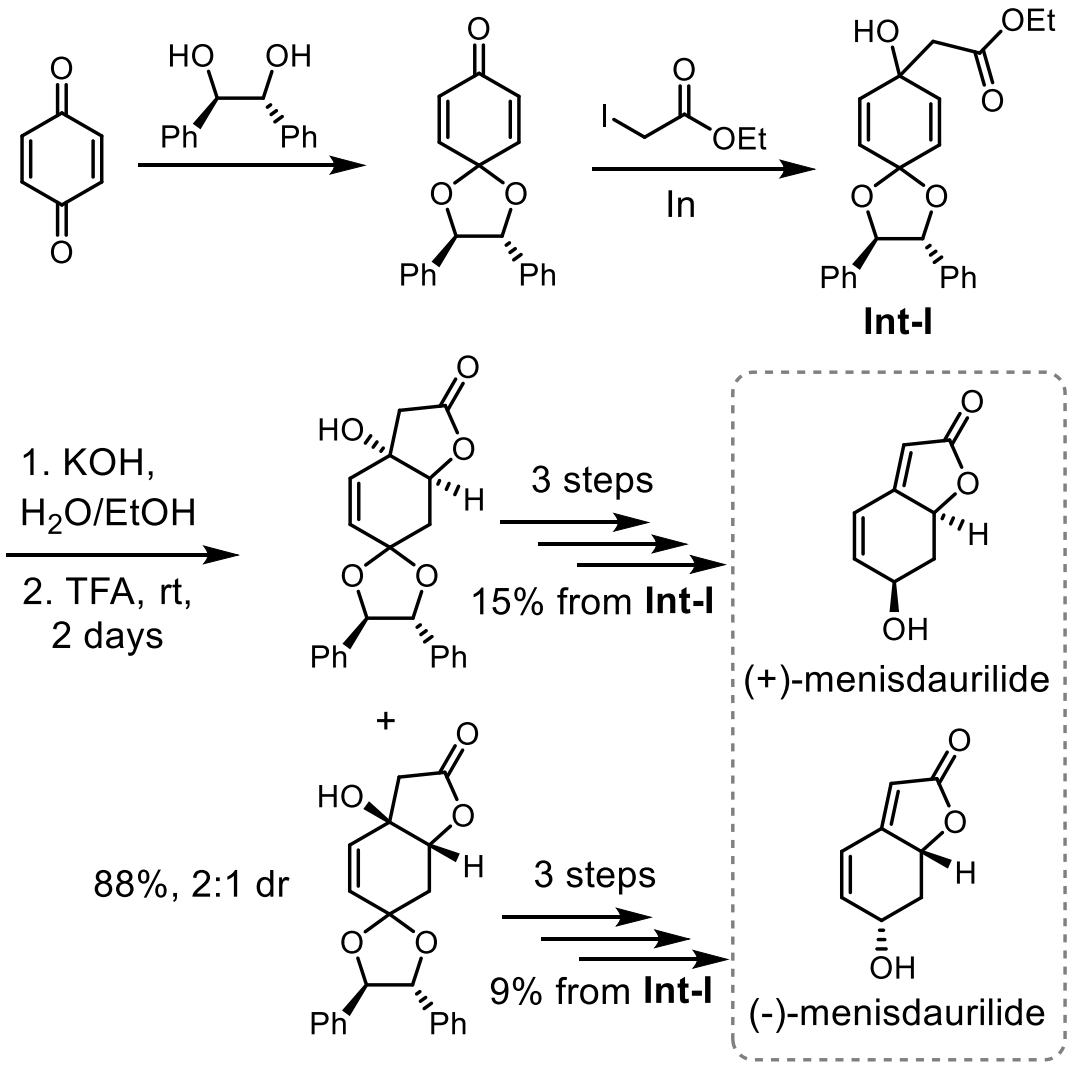
Org. Lett. **2001**, 3 ,703–706.

Bio-inspired Synthesis From (+)-Menisdaurilide

First syntheses of both enantiomers of menisdaurilide from quinone (Busque, de Marche, 2008):

One enantiomer was pushed forward in the first "bio-inspired" synthesis of a *Securinega* alkaloid allosecurinine:

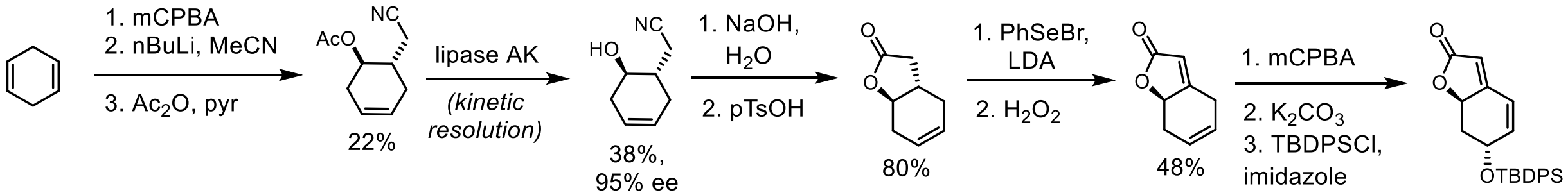




J. Org. Chem. **2008** 73, 19. *Tetrahedron: Asymmetry* **2003**, 14, 2021–2032.

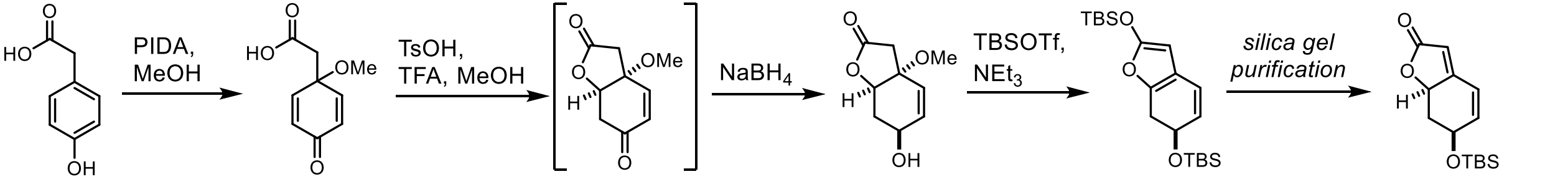
Improved Syntheses of Menisdaurilide and Aquilegiolide

An improved synthesis of (+)-aquilegiolide allows more efficient access to key siloxyfuran (Gademann, 2013):



50%, 5:1 dr

Rapid one-pot access to racemic menisdaurilide for bioinspired synthesis (Quideau, 2019):



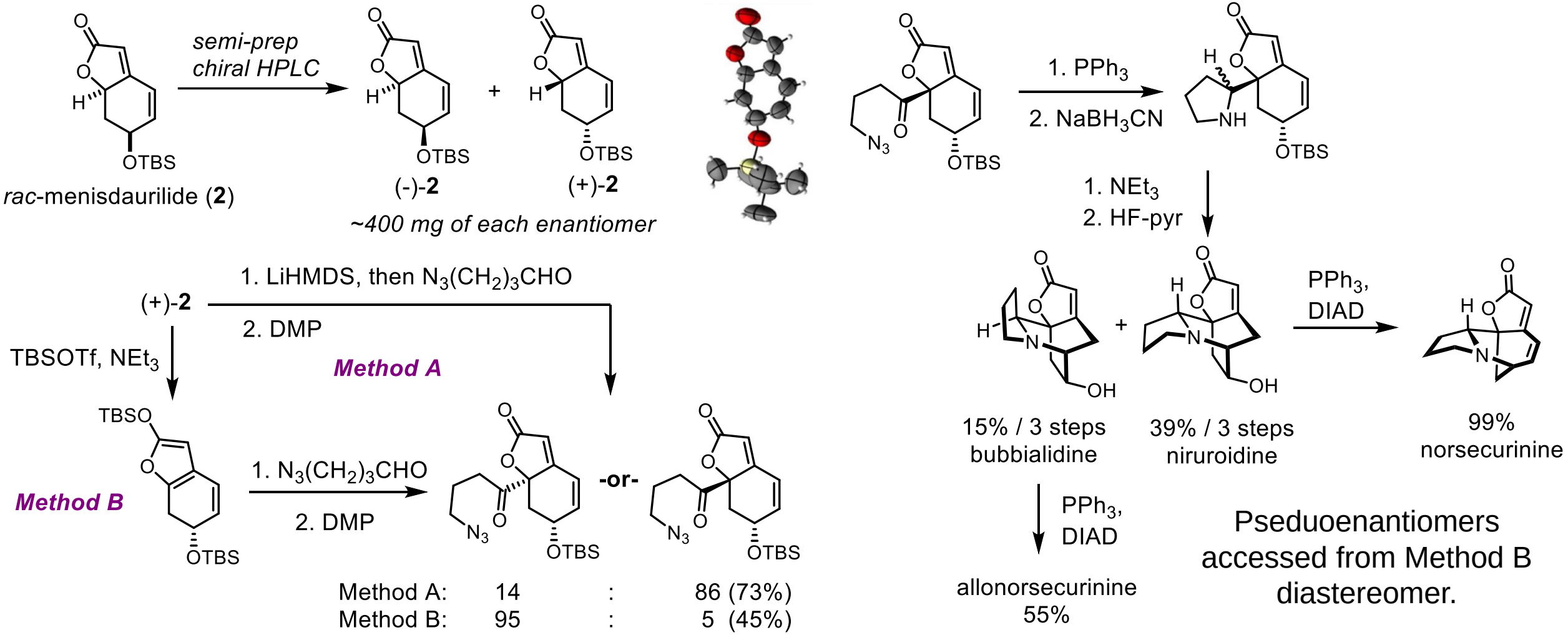
28% / 5 steps, >95:5 dr

rac-menisdaurilide

Although it is racemic, this route can provide ~2.5 g of material per day with only one column.

Bio-Inspired Synthesis of 12 Alkaloids via Menisdaurilide Route

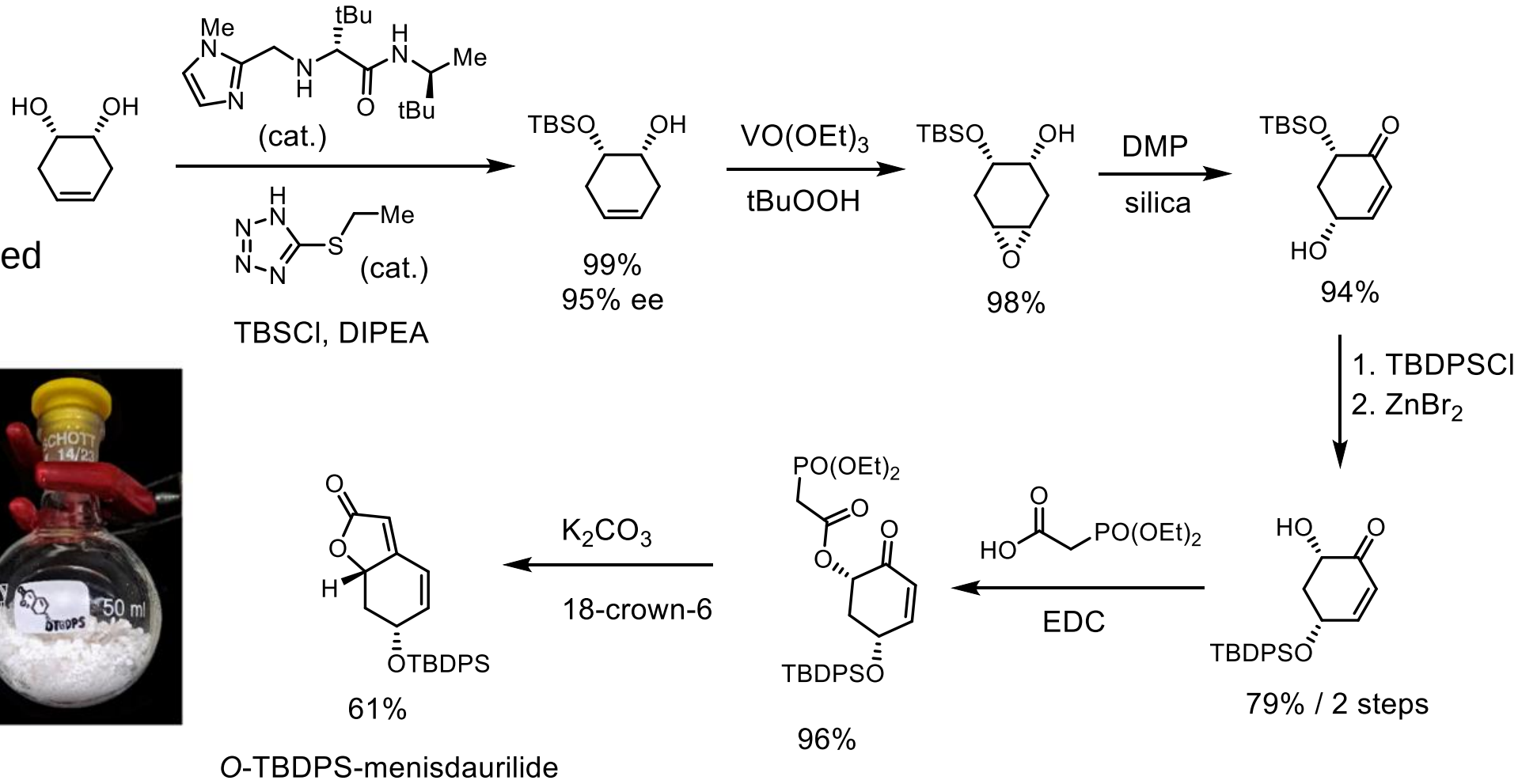
Diastereoselective Mukaiyama aldol additions based on choice of enolization conditions:



Chem. Eur.J. **2019**, *25, 11574 - 11580.*

The Best Synthesis of Menisdaurilide?

Large-scale enantioselective synthesis of protected menisdaurilide by catalytic desymmetrization (Han, 2022):

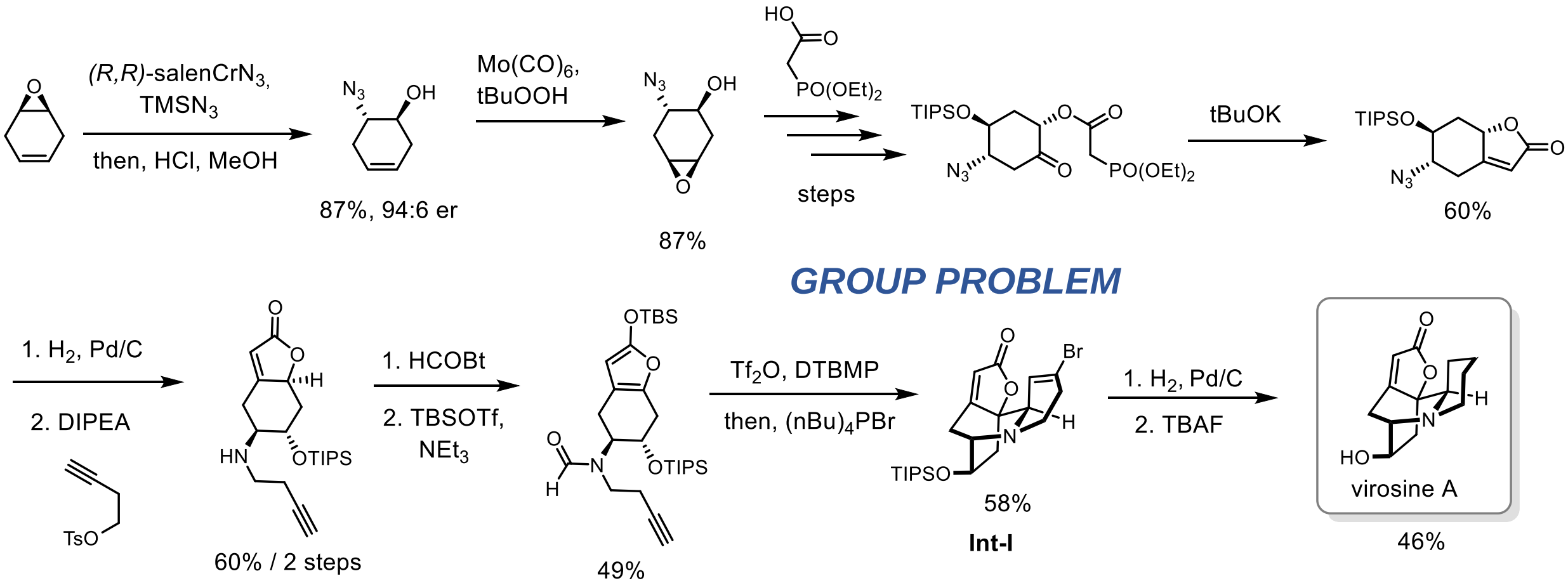


The route was completed on >20 g scale!

Nature **2006**, 443, 67–70. *Nature Comm.* **2022**, 13, 5149.

Menisdaurilide-Type Route with Key Desymmetrization

First enantioselective synthesis of virosine A using Approach 2 (Belanger, 2012):

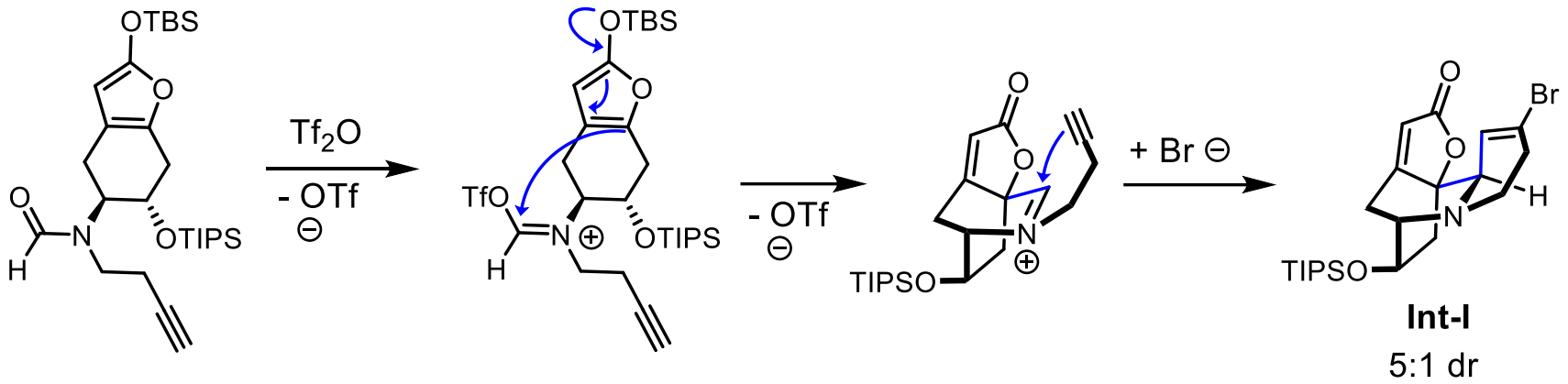


Mechanism of formation of **Int-I**?

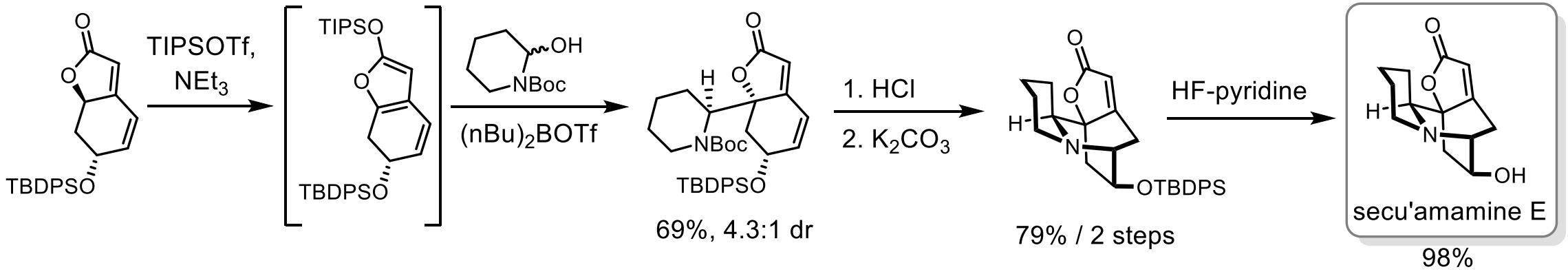
J. Org. Chem. **2012**, 77, 3215−3221.

Menisdaurilide-Type Route with Key Desymmetrization

Mechanism of formation of **Int-I** by Vilsmeier-Haack vinylagous Mukaiyama-Mannich reactions:



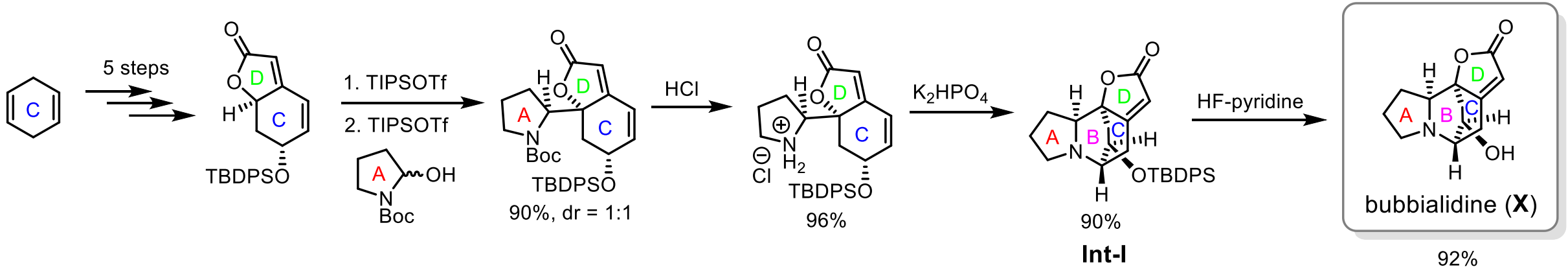
Synthesis of secu'amamine E (*ent*-virosine A) by vinylagous Mukaiyama-Mannich reaction (Gademann, 2017):



J. Org. Chem. **2012**, 77, 3215−3221.

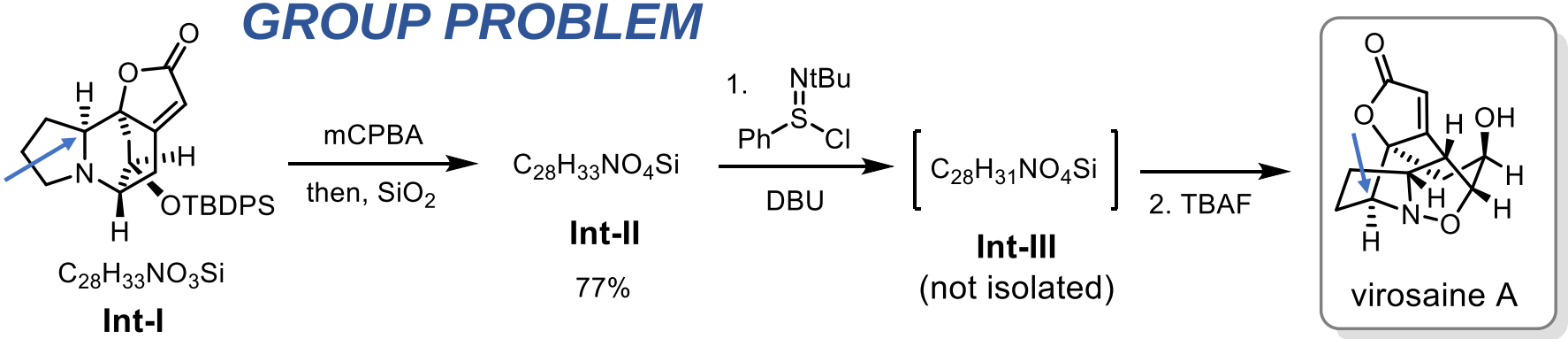
Total Synthesis of Bubbialidine and Virosaine A

First total synthesis of bubbialidine with key A-ring installation step by vinylogous Mukaiyama-Mannich reaction:



Strategy to access "birdcage" virosaine motif demonstrated in the divergent synthesis of virosaine A from **Int-I**:

GROUP PROBLEM



- Mechanism of formation and structure of **Int-II**?
- Structure of **Int-III**?
- Mechanism of formation of virosaine A from **Int-III**?

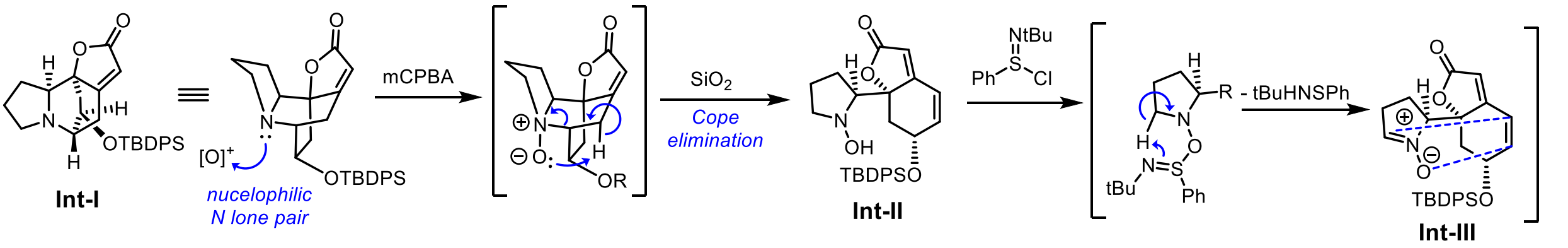
Hint 1: No formal charges in **Int-II**

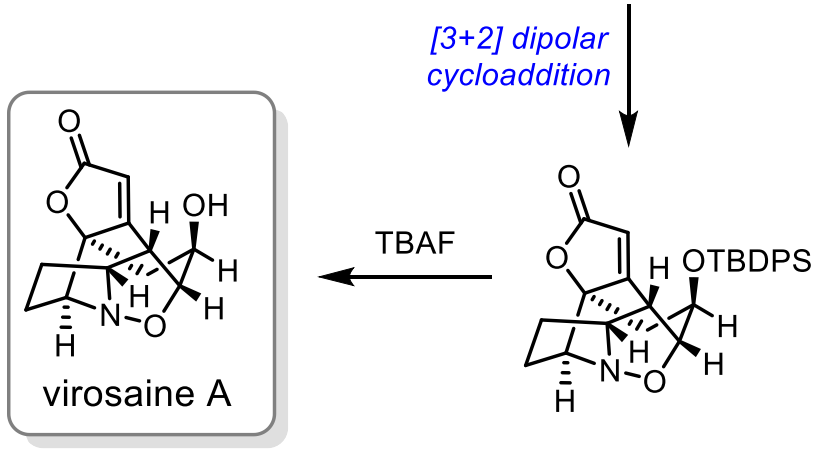
Hint 2: Follow C2 in A ring

Chem. Commun. **2013**, 49, 1921-1923.

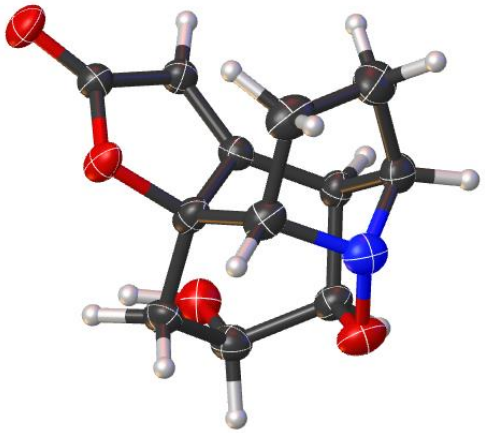
Total Synthesis of Bubbialidine and Virosaine A

This report demonstrated viable [3+2] dipolar cycloaddition from *in situ* nitrone to access birdcage virosaine A:





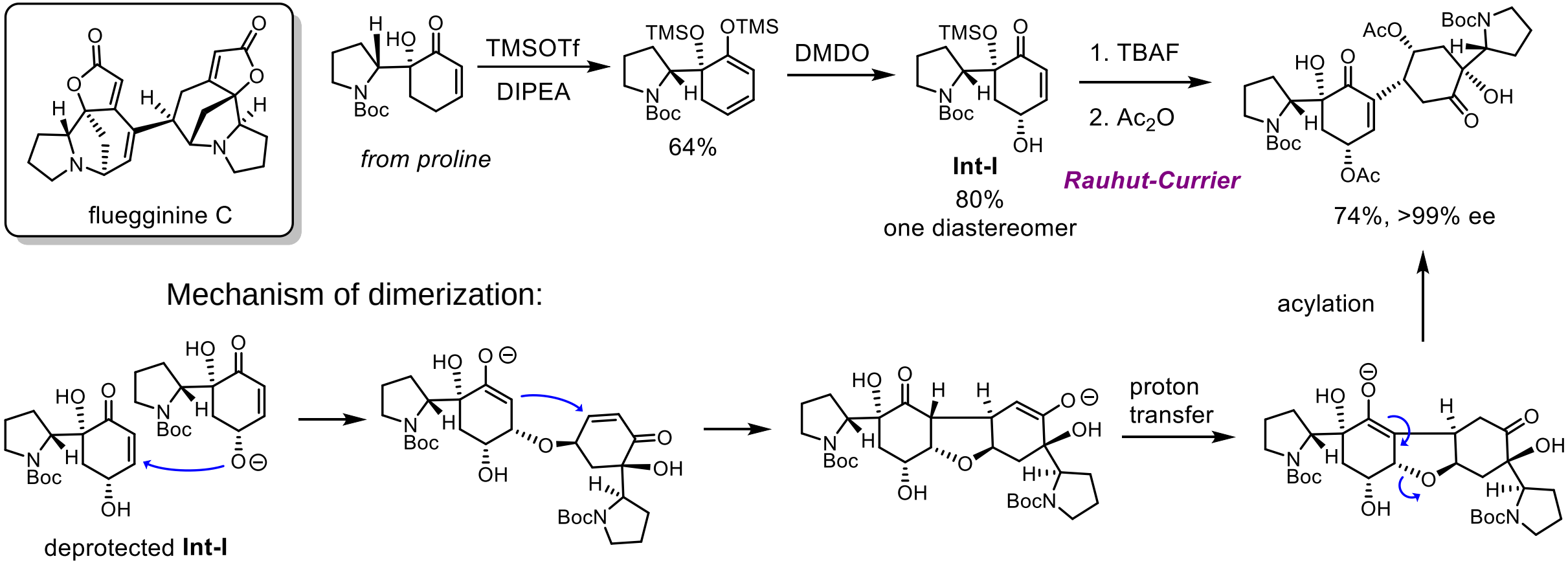
A similar [3+2] cycloaddition strategy was used for the synthesis of virosaine B (Li, 2013), the C2 pseudoenantiomer of virosaine A.



Chem. Commun. **2013**, 49, 1921-1923. *Angew. Chem. Int. Ed.* **2013**, 52, 620 –624.

Higher-Order *Securinega* Alkaloids

Total synthesis of the higher-order alkaloid fluegginine C by Rauhut-Currier dimerization (Han, 2017):

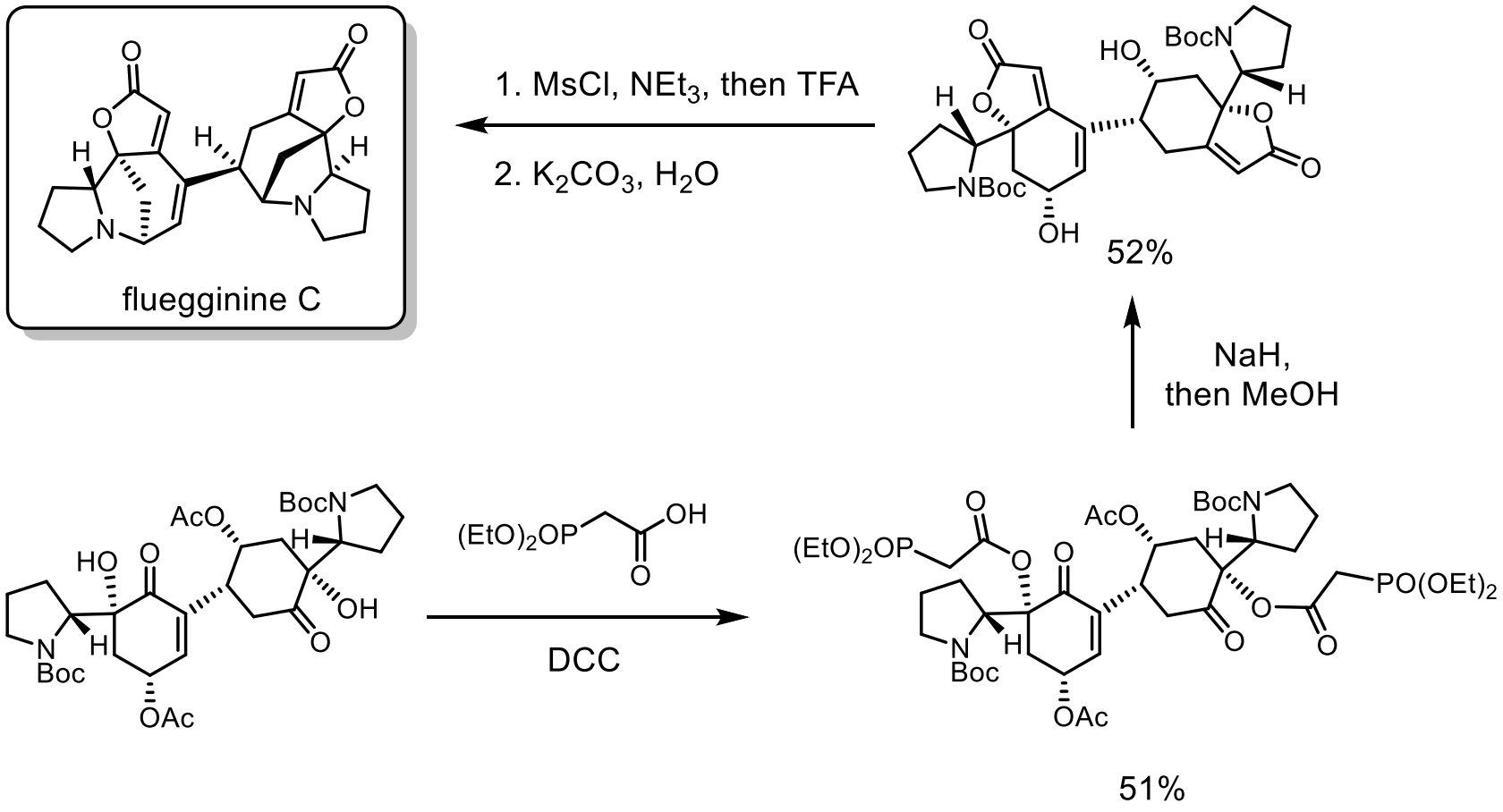


Mechanism of dimerization:

J. Am. Chem. Soc. **2017**, 139, 6302−6305.

Higher-Order *Securinega* Alkaloids

Total synthesis of the higher-order alkaloid fluegginine C by Rauhut-Currier dimerization (Han, 2017):



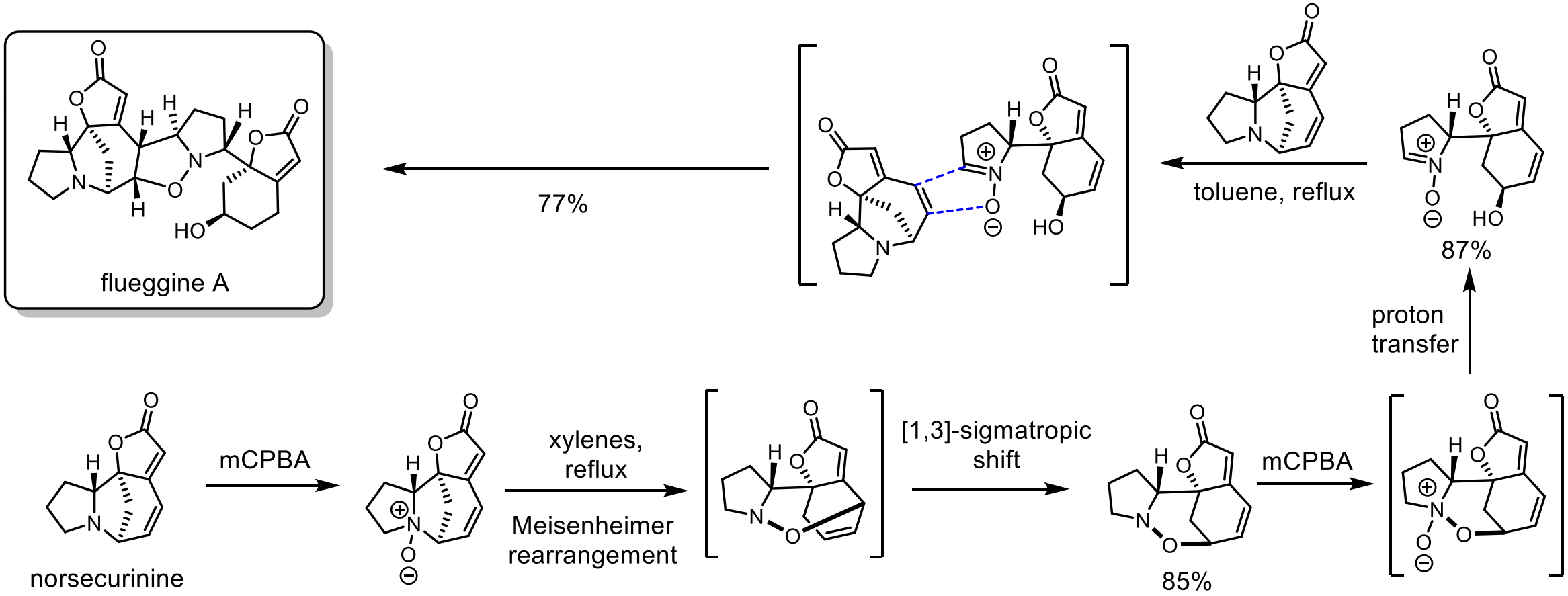
The authors hypothesize that all dimeric and oligomeric *Securinega* alkaloids are produced by enzymatic Rauhut-Currier reactions.

This is an appealing possibility for dimers with no additional oxygenation, but might not be true for dimers derived from oxidized monomers

J. Am. Chem. Soc. **2017**, 139, 6302−6305.

Higher-Order *Securinega* Alkaloids

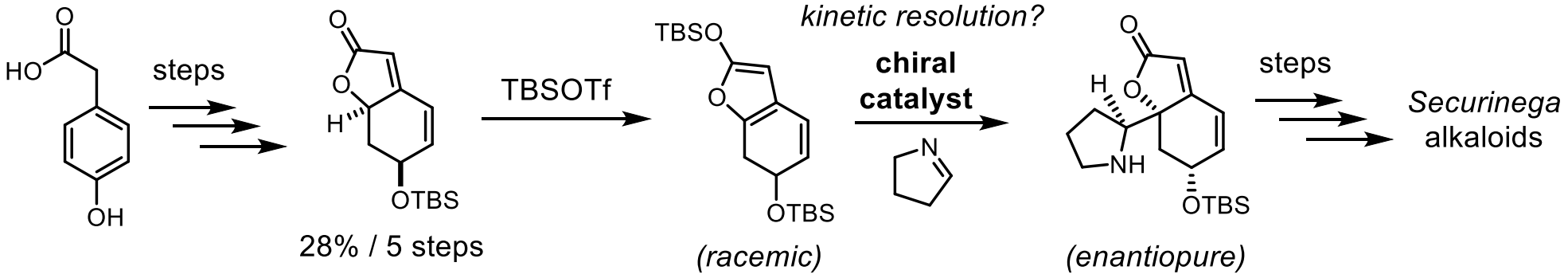
Total synthesis of the higher-order alkaloid flueggine B by intermolecular [3+2] cycloaddition (Li, 2013):



Summary and Outlook

- Synthesis of monomeric alkaloids is well established. Highly efficient routes based on tandem RCM processes or derivatization of menisdaurilide/aquilegiolide have been developed.

- Catalytic desymmetrization methods are the state-of-the-art for Mukaiyama-type constructions. Possible future direction – combine Quideau's high-yielding one-pot synthesis of *rac*-menisdaurilide with Mukaiyama-Mannich KR to construct key C2-C9/10 bond:

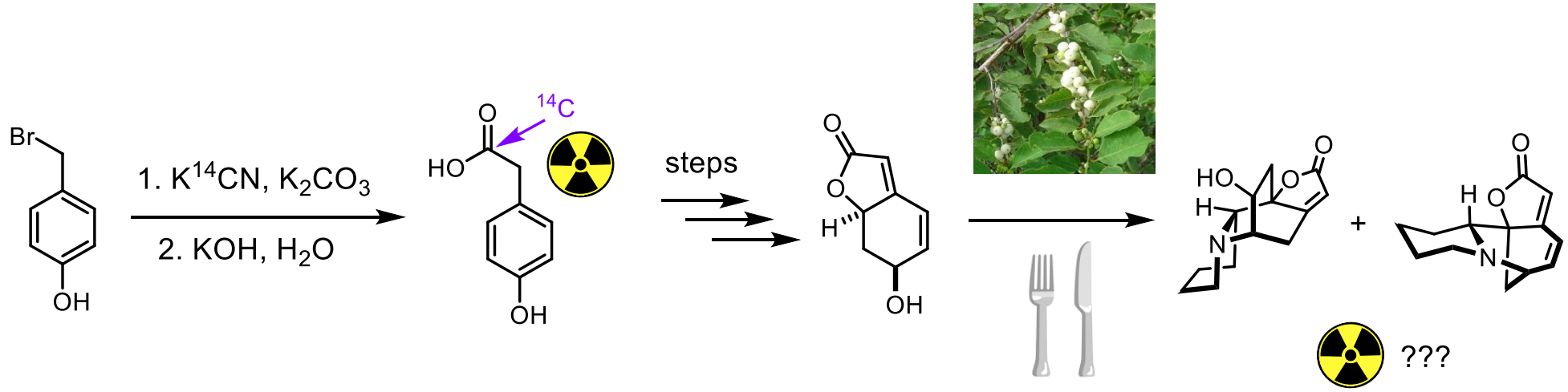


- The synthesis of higher-order and highly oxidized alkaloids is much less explored.

- (My opinion) This class of natural products desperately needs a new, unified nomenclature system... Names are given by the isolation chemists in an *ad hoc* manner, and there is little rationality in the naming. A new naming system with consideration of the (pseudo)enantiomorphism of the class should be developed.

Summary and Outlook

- Lastly, the phytochemistry of *F. virosa* is fascinating and needs much more exploration. Feeding ^{14}C labelled menisdaurilide to the plant could prove Gademann's biosynthetic hypothesis:



Any ^{14}C incorporation into alkaloid products demonstrates that menisdaurilide is a viable biosynthetic intermediate. Incorporation of ^{14}C into BOTH neosecuranine- and securinine-type alkaloids would conclusively demonstrate that these intermediates are part of the same biosynthetic pathway, and that they diverge after the plant produces menisdaurilide.

Useful Reviews/Book Chapters

ACES Asian Chemical Editorial Society
DOI: 10.1002/ajoc.201700142
ASIAN JOURNAL OF ORGANIC CHEMISTRY
Focus Review

Natural Product Synthesis

SPECIAL ISSUE

Securinega Alkaloids: Complex Structures, Potent Bioactivities, and Efficient Total Syntheses

Robin Wehlauch and Karl Gademann*[a]

Asian J. Org. Chem. **2017**, 6, 1146–1159.

CHAPTER ONE

The *Securinega* Alkaloids

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[1]Corresponding author: E-mail: francois-hugues.poree@parisdescartes.fr

The Alkaloids, Vol. 74 (Ed.:H.-J.Knolker), Academic Press, London, **2015**, pp. 1–120.

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Article

Synthesis of High-Order and High-Oxidation State *Securinega* Alkaloids

Gyumin Kang, Sangbin Park, and Sunkyu Han*

Cite This: *Acc. Chem. Res.* 2023, 56, 140–156
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