

The Story of Hyperforin

Exploring Path to Concise Synthesis

Presenter: Jiaxin Xie

Advisor: Prof. Dong

The University of Texas at Austin

If a man keeps cherishing his old knowledge, so as continually to be acquiring new, he may be a teacher of others. -----Confucius

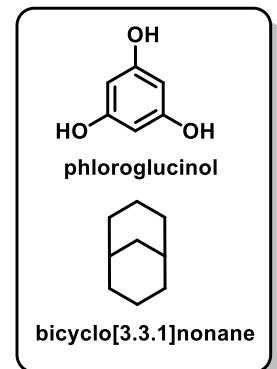
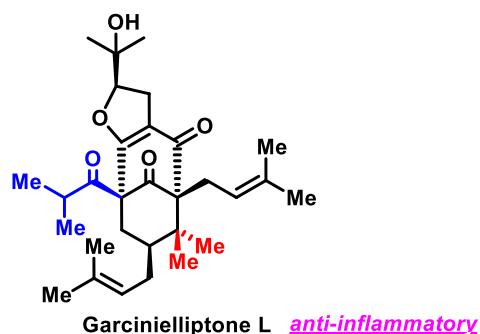
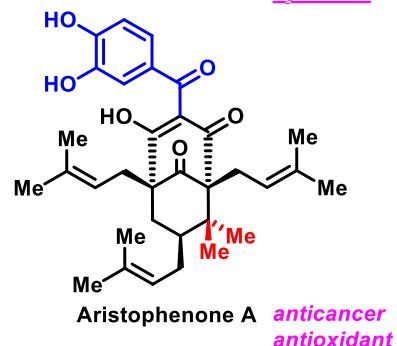
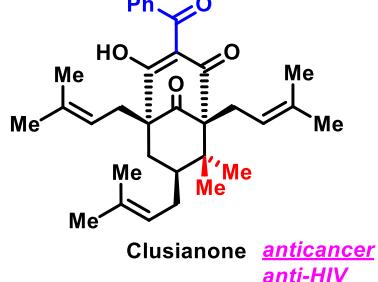
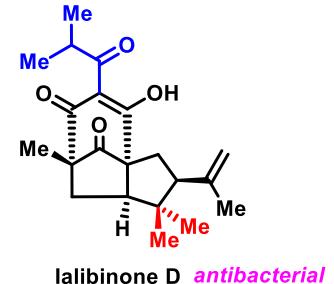
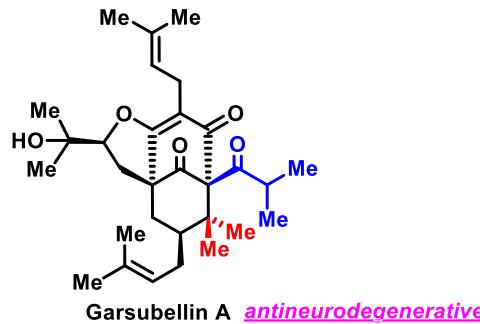
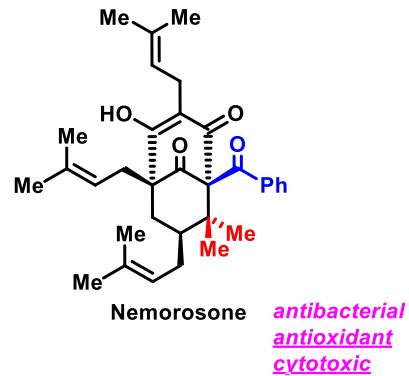
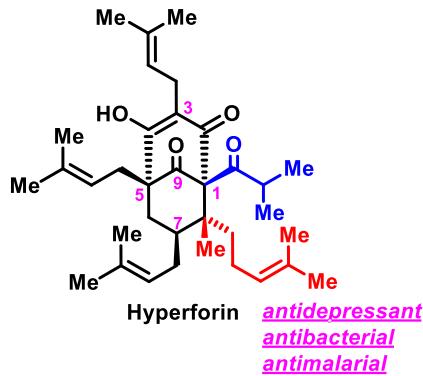
The Story of Hyperforin

Part 1. A Brief Introduction of PPAPs

- **PPAPs:** Polycyclic Polyprenylated Acylphloroglucinols
- **Isolation:** mainly from *Hypericum perforatum* (贯叶连翘) and other plants from the family *Guttiferae* (金丝桃科) and related families; over **150** natural products
- **Structural features:** bicyclo[3.3.1]nonane or bicyclo[3.2.1]octane

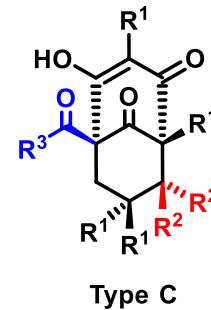
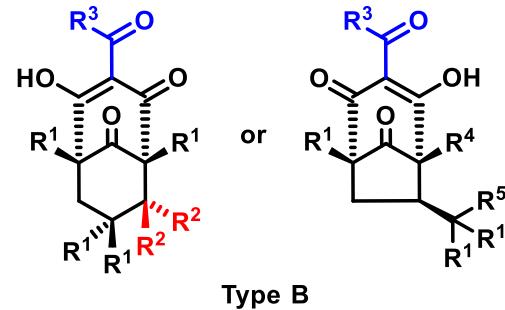
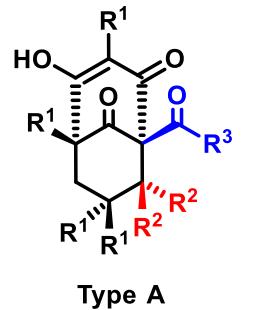


Hypericum perforatum
(St. John's wort)



Part 1. A Brief Introduction of PPAPs

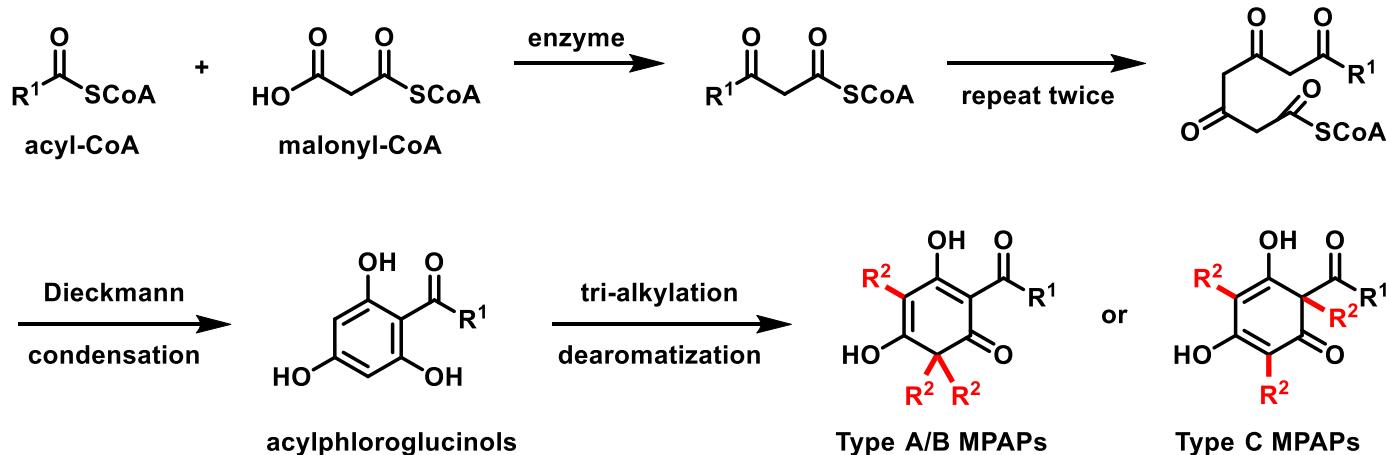
➤ 3 Classes of PPAPs



$R^1 = \text{Me, prenyl, geranyl; } R^2 = \text{Me, geranyl, etc.; } R^3 = i\text{Pr, Ph, etc.}$

➤ Biosynthesis of PPAPs

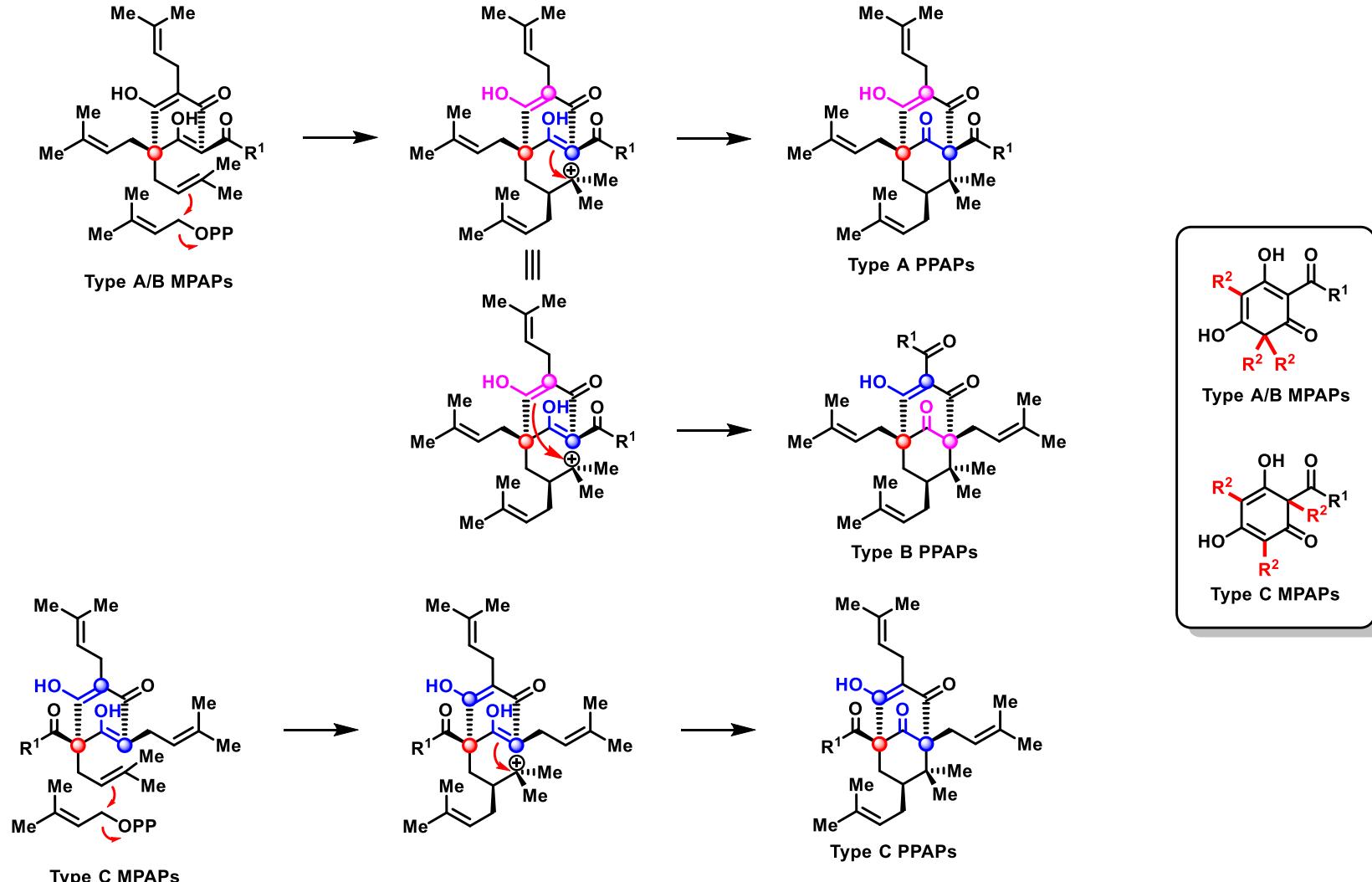
Stage 1: Biosynthesis of MPAPs from CoAs



The Story of Hyperforin

Part 1. A Brief Introduction of PPAPs

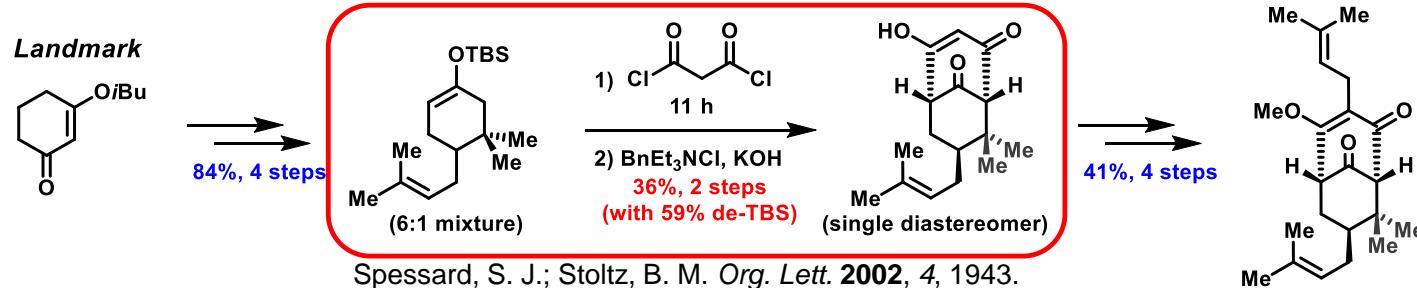
Stage 2: Biosynthesis of PPAPs from MPAPs ($R^2 = \text{prenyl}$)



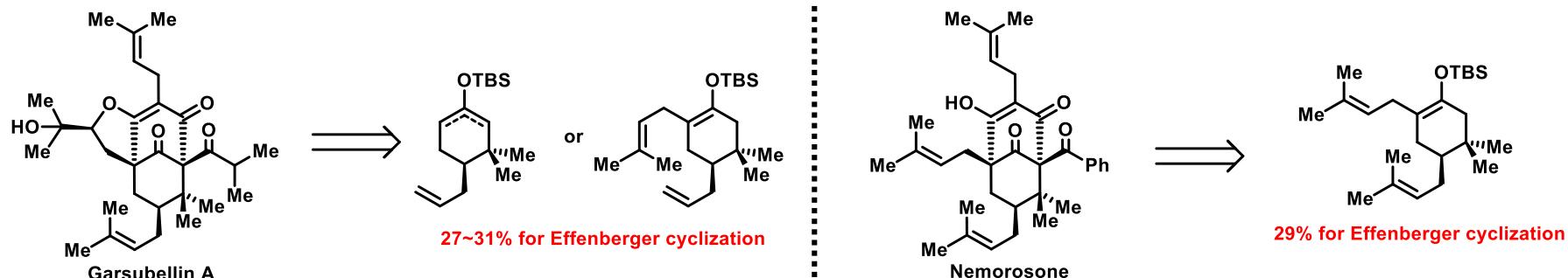
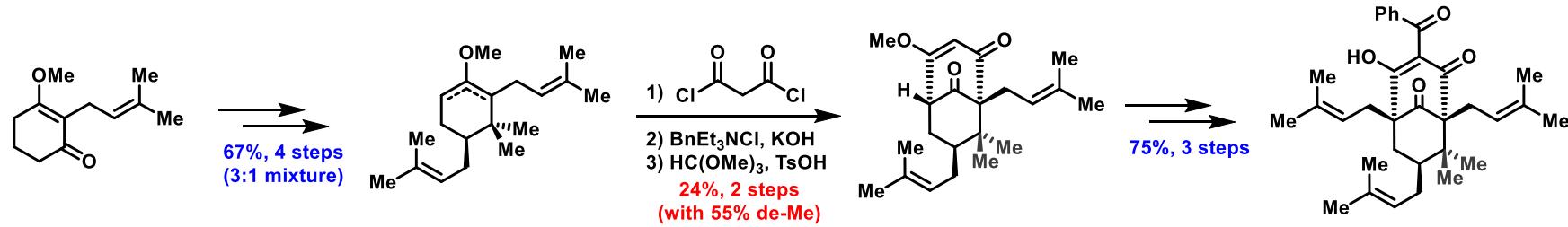
The Story of Hyperforin

Part 2. Synthetic Strategies towards bicyclo[3.3.1]nonane

➤ Stoltz's Preliminary Work (2002): *Effenberger Cyclization Approach*

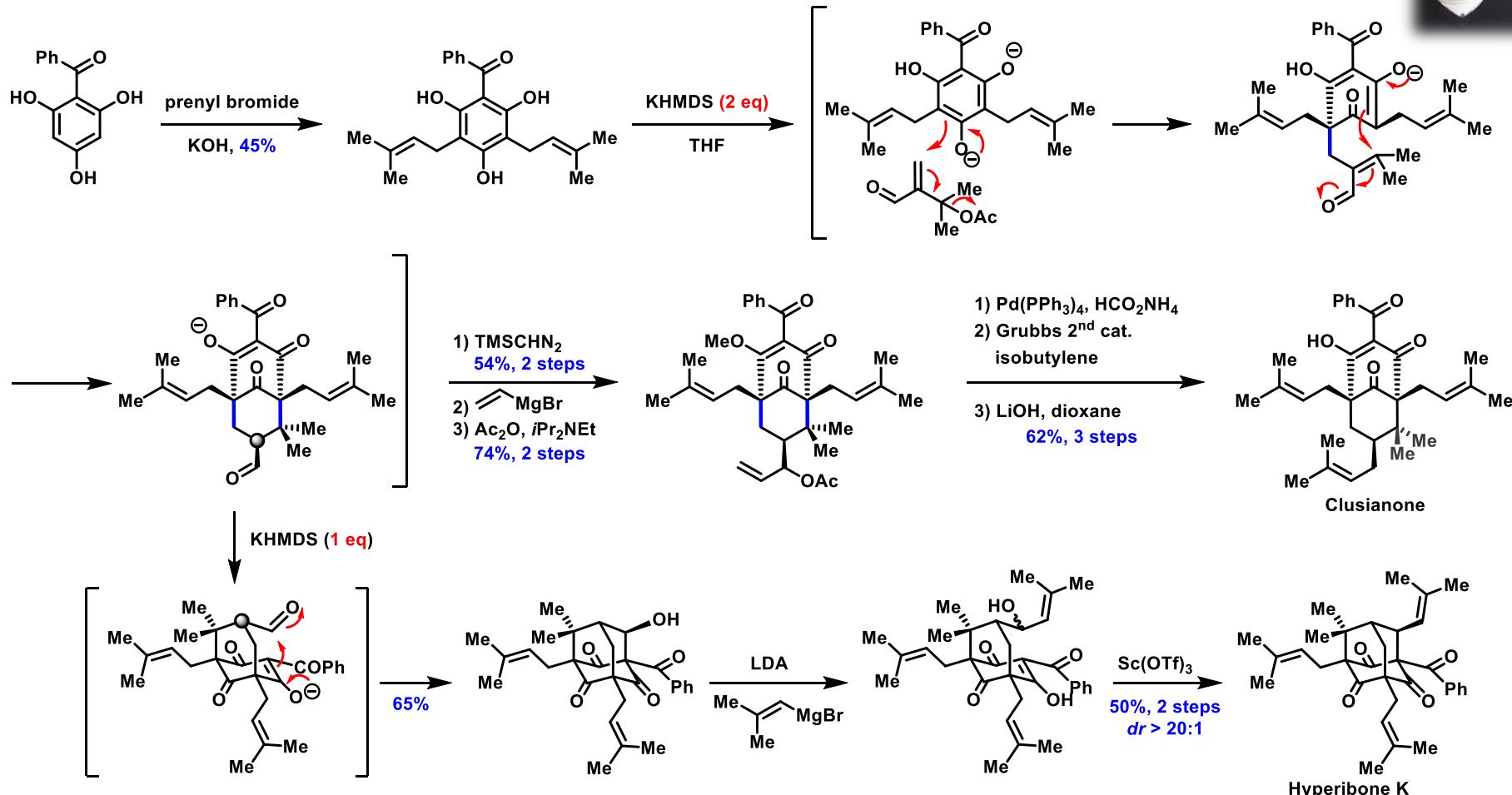


➤ Simpkins' Syntheses of (\pm)-Clusianone, (\pm)-Garsubellin A, and (\pm)-Nemorosone



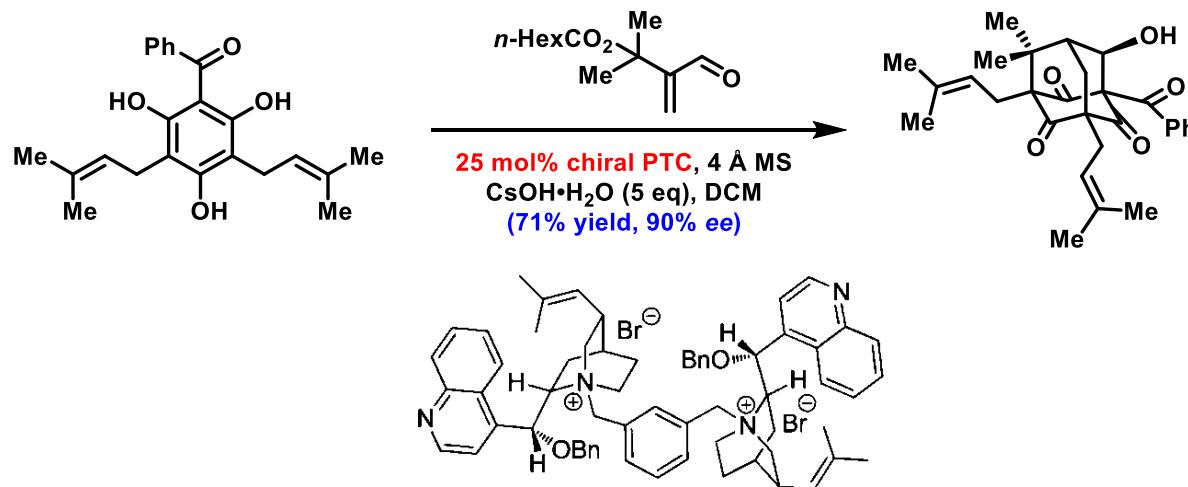
Part 2. Synthetic Strategies towards bicyclo[3.3.1]nonane

➤ Porco's Biomimetic Synthesis: *Dearomatization / Annulation Strategy*



Part 2. Synthetic Strategies towards bicyclo[3.3.1]nonane

- Porco's Biomimetic Synthesis: *Dearomatization / Annulation Strategy*



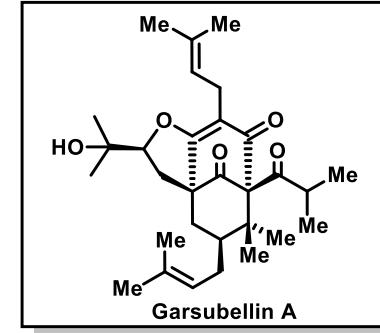
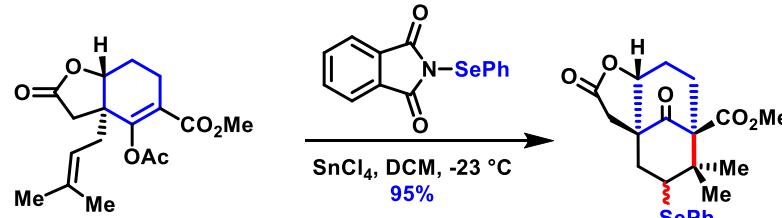
Qi, J.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2007**, 129, 12682.

Qi, J.; Beeler, A. B.; Zhang, Q.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2010**, 132, 13642.

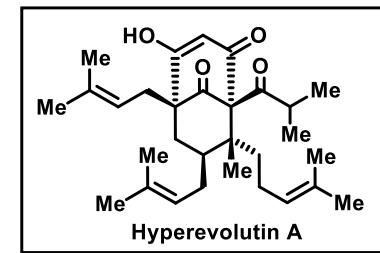
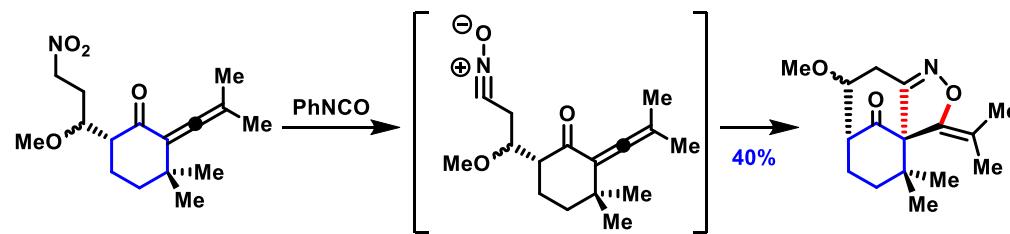
Part 2. Synthetic Strategies towards bicyclo[3.3.1]nonane

➤ Miscellaneous Synthetic Strategies

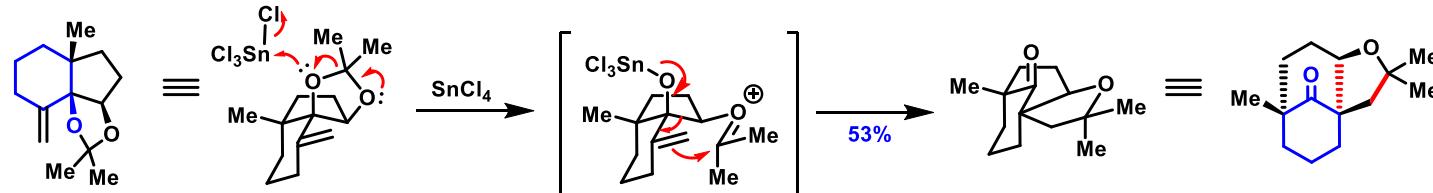
1999, Nicolaou's Selenium-mediated Cyclization



2002, Young's Intramolecular [3+2] Cycloaddition



2005, Barriault's Cationic Cyclization Cascade



Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724.

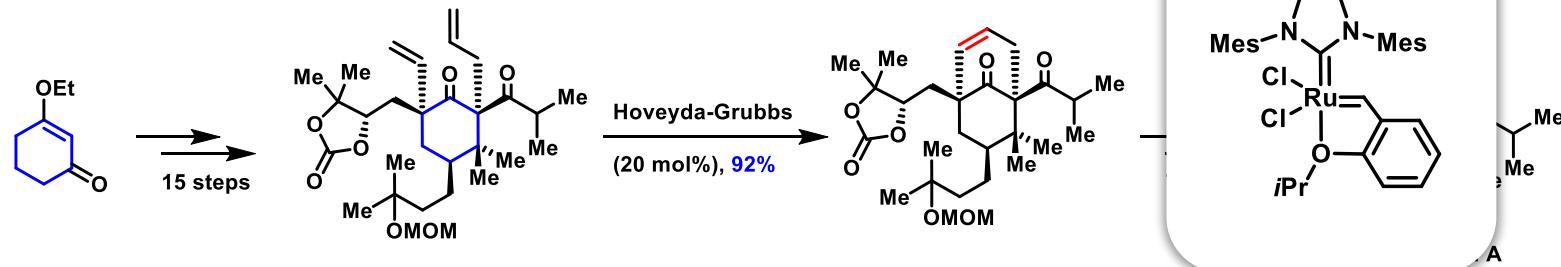
Young, D. G. J.; Zeng, D. *J. Org. Chem.* **2002**, *67*, 3134.

Lavigne, R. M. A.; Riou, M.; Girardin, M.; Morency, L.; Barriault, L. *Org. Lett.* **2005**, *7*, 5921.

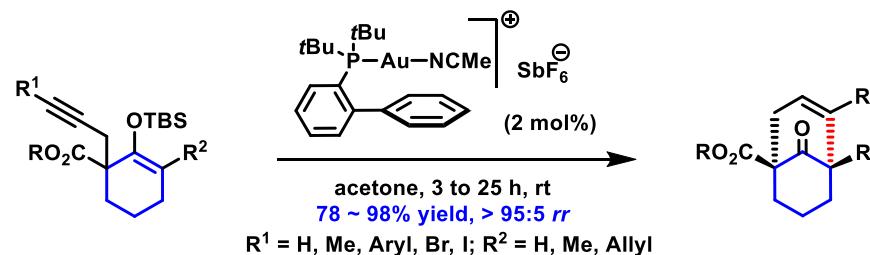
Part 2. Synthetic Strategies towards bicyclo[3.3.1]nonane

➤ Miscellaneous Synthetic Strategies

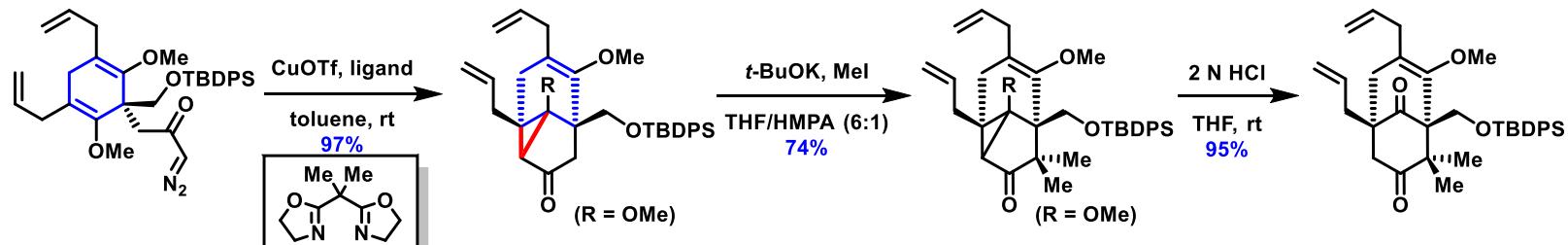
2005, Shibasaki's Ring-Closing Metathesis Strategy



2009, Barriault's Gold-Catalyzed 6-endo-dig Cyclization



2010, Nakata's Intramolecular Cyclopropanation/Fragmentation Approach



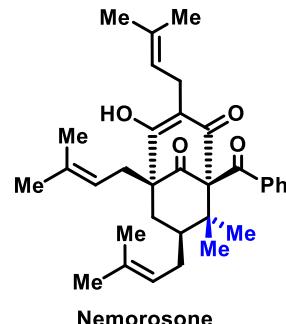
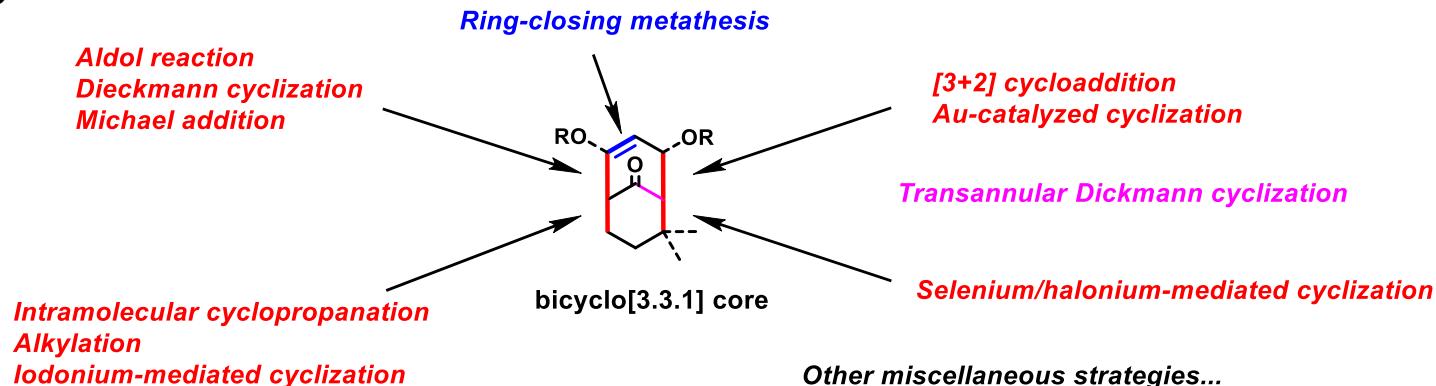
Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, 127, 14200.

Mitasev, B.; Be'tournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, 11, 4236.

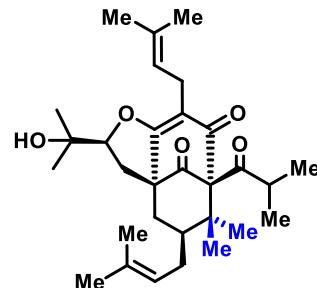
Abe, M.; Saito, A.; Nakata, M. *Tetrahedron Lett.* **2010**, 51, 1298.

Part 2. Synthetic Strategies towards bicyclo[3.3.1]nonane

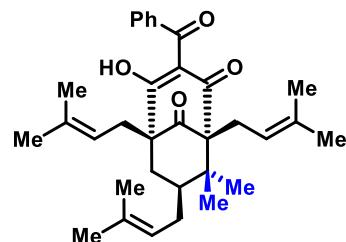
➤ Summary



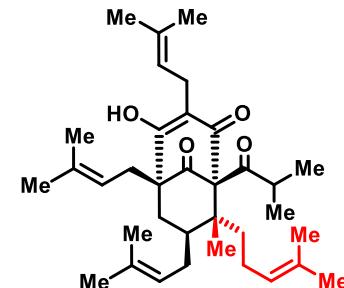
Nemorosone
4 total syntheses (1 enantioselective)
(from 2007 to 2015)
several formal syntheses



Garsubellin A
4 total syntheses
(from 2005 to 2013)
several formal syntheses
a number of synthetic studies



Clusianone
8 total syntheses (4 enantioselective)
(from 2007 to 2015)
several formal syntheses
a number of synthetic studies



Hyperforin
5 total syntheses (2 enantioselective)
(from 2010 to 2015)

a number of total syntheses of epi-PPAPs...

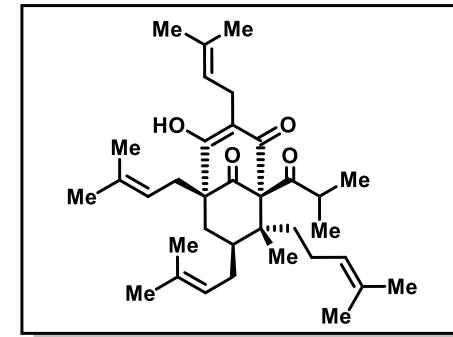
Danishefsky, Nakata, Porco, Shair, Shibasaki, Simpkins, et al.

Part 3. Introduction of Hyperforin

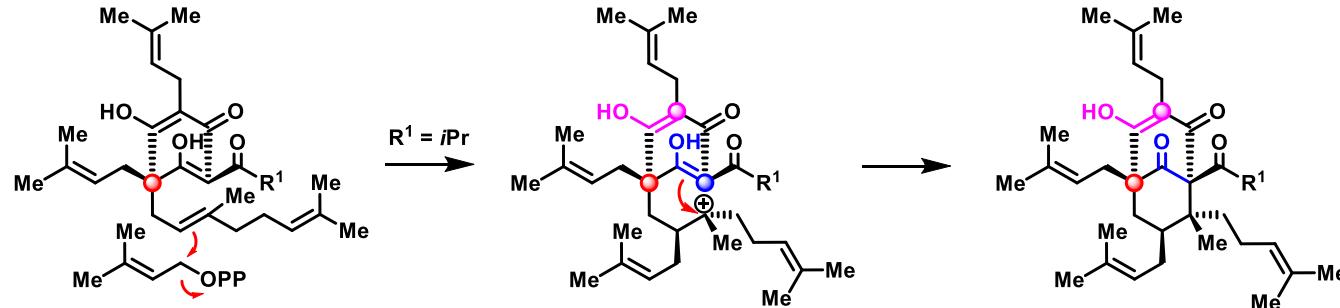
- Isolated from ***Hypericum perforatum*** (*St. John's wort*) in 1971;
- Structure disclosed in 1975;
- Responsible for **antidepressant** activity of the herb (*St. John's wort*)
Mechanism: block the re-uptake of a variety of neurotransmitters by **selectively activating TRPC6** (classical transient receptor potential protein), which leads to a cellular influx of Na^+ and Ca^{2+} , diminishing membrane electrochemical gradient (indirectly inhibiting neuronal neurotransmitter reuptake) and triggering cell differentiation;
- **Anti-bacterial** activity against multi-resistant *Staphylococcus aureus* and other Gram-positive bacteria;
- Highly oxidized **bicyclo[3.3.1]nonane** core;
Densely substituted with **terpenoid side chains**;
- 5 total syntheses by **Shibasaki (2010)**, **Nakata (2013)**, **Shair (2013)**, **Barriault (2014)**, **Maimone (2015)**, respectively.



Hypericum perforatum
(*St. John's wort*)



➤ Biosynthesis (Stage 2)



Part 4. Shibasaki's Total Synthesis of *ent*-Hyperforin

➤ Professor Masakatsu Shibasaki



柴崎 正勝

Research Interests:

- Asymmetric Catalysis
- Total Synthesis
- Drug Design

Biography:

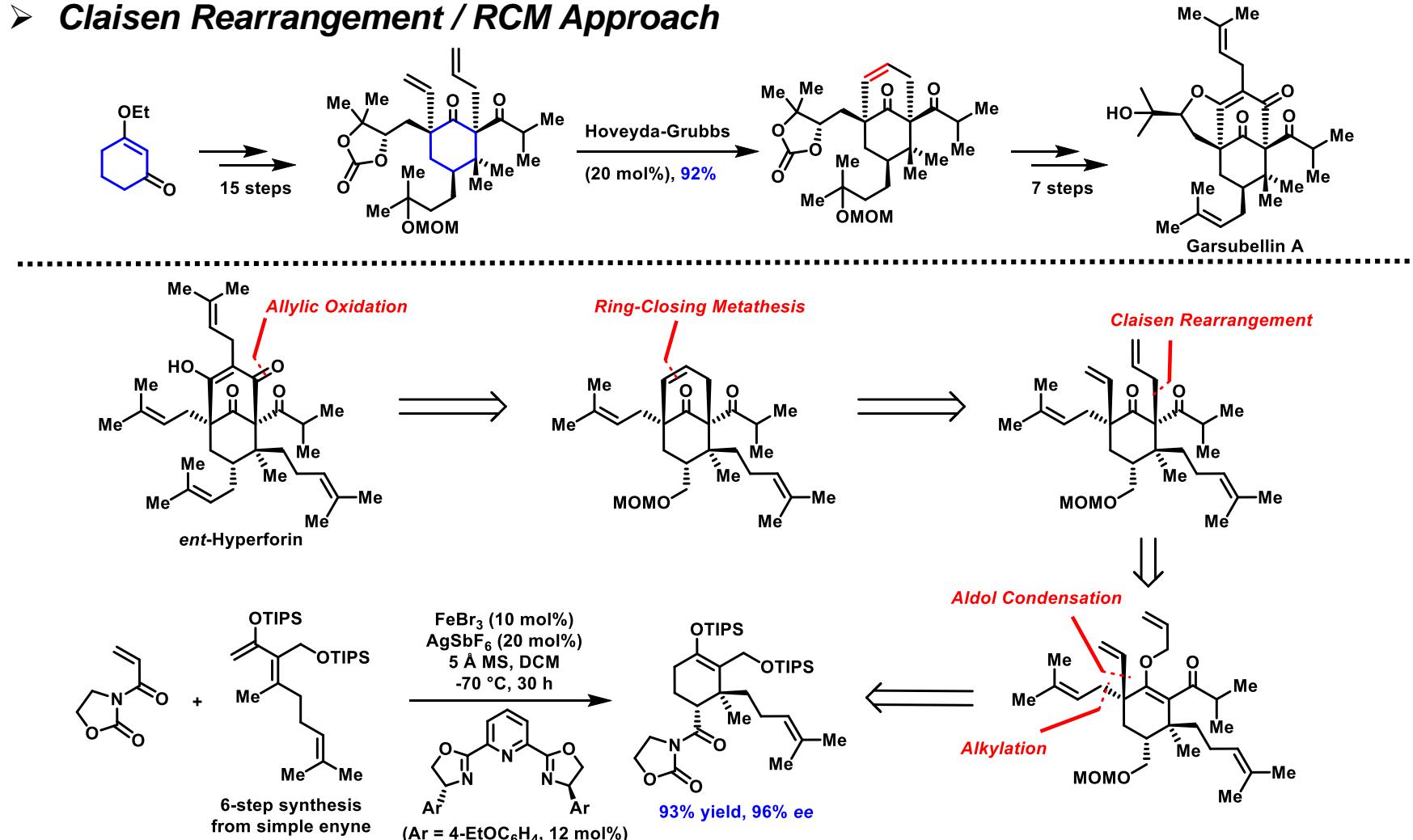
- 1974: University of Tokyo, **Ph.D.**
Research advisor: Prof. Shun-ichi Yamada
- 1974-1977: Harvard University, **Post-doctoral fellow**
Research advisor: Prof. E. J. Corey
- 1977-1983: Teikyo University, **Associate Professor**
(Prof. Shiro Ikegami)
- 1983-1986: Sagami Chemical Research Center, **Research group leader**
- 1986-1991: Hokkaido University, **Professor**
- 1991-2010: University of Tokyo, **Professor**
- 2010-present: University of Tokyo/Hokkaido University, **Professor Emeritus**

Publications and Citations:

- 512 publications (1971-2010)
- 1 Science, 98 JACS, 31 ACIE,
- 3985 citations for **asymmetric catalysis** (1995-2005)
Noyori (2533), Hayashi (2452), Jacobsen (2449), Trost (2291)
(Source: Thomson)

Part 4. Shibasaki's Total Synthesis of *ent*-Hyperforin

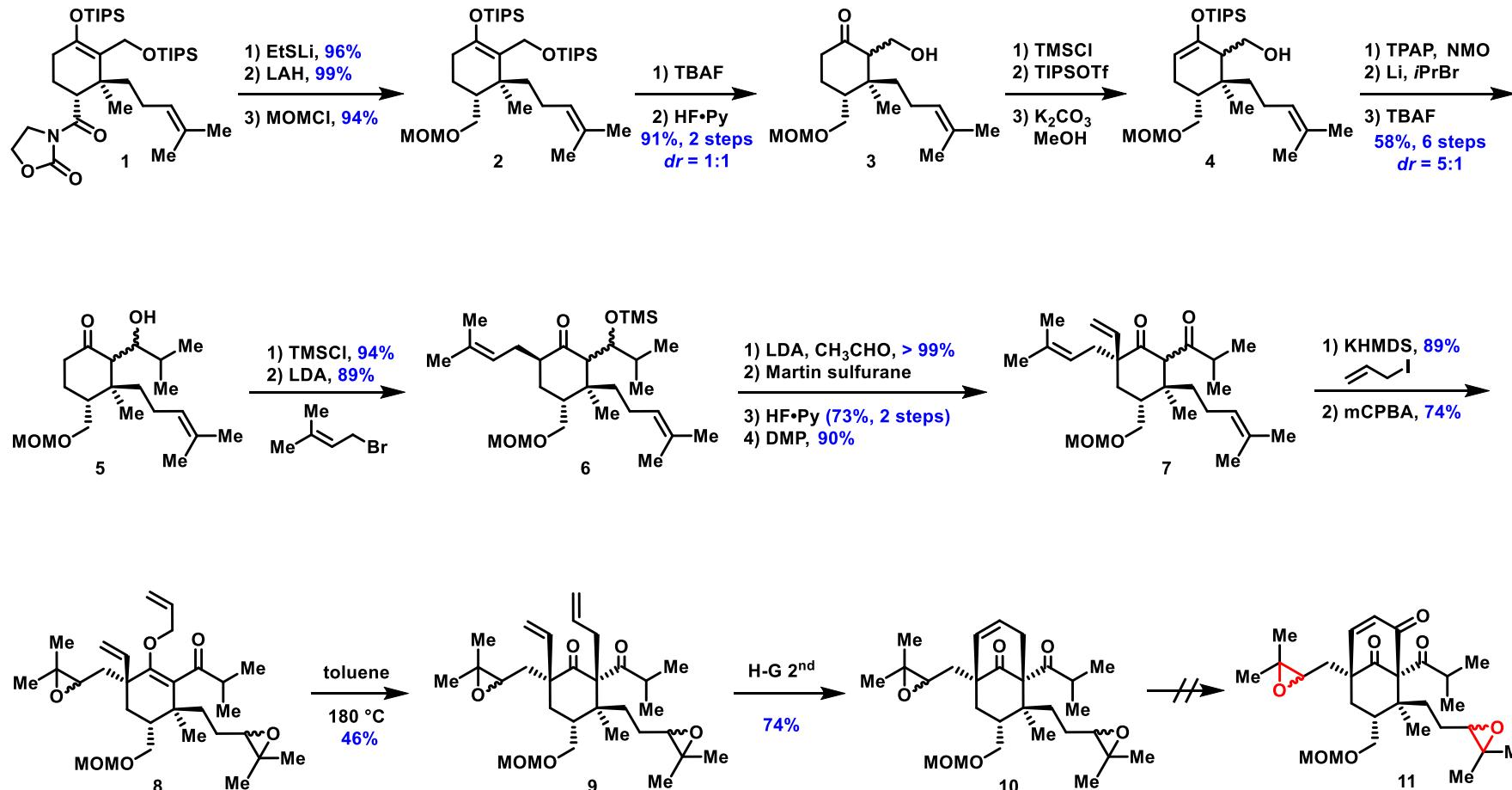
➤ Claisen Rearrangement / RCM Approach



Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, 127, 14200.
 Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, 49, 1103.
 Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2010**, 66, 6569.

Part 4. Shibasaki's Total Synthesis of Hyperforin

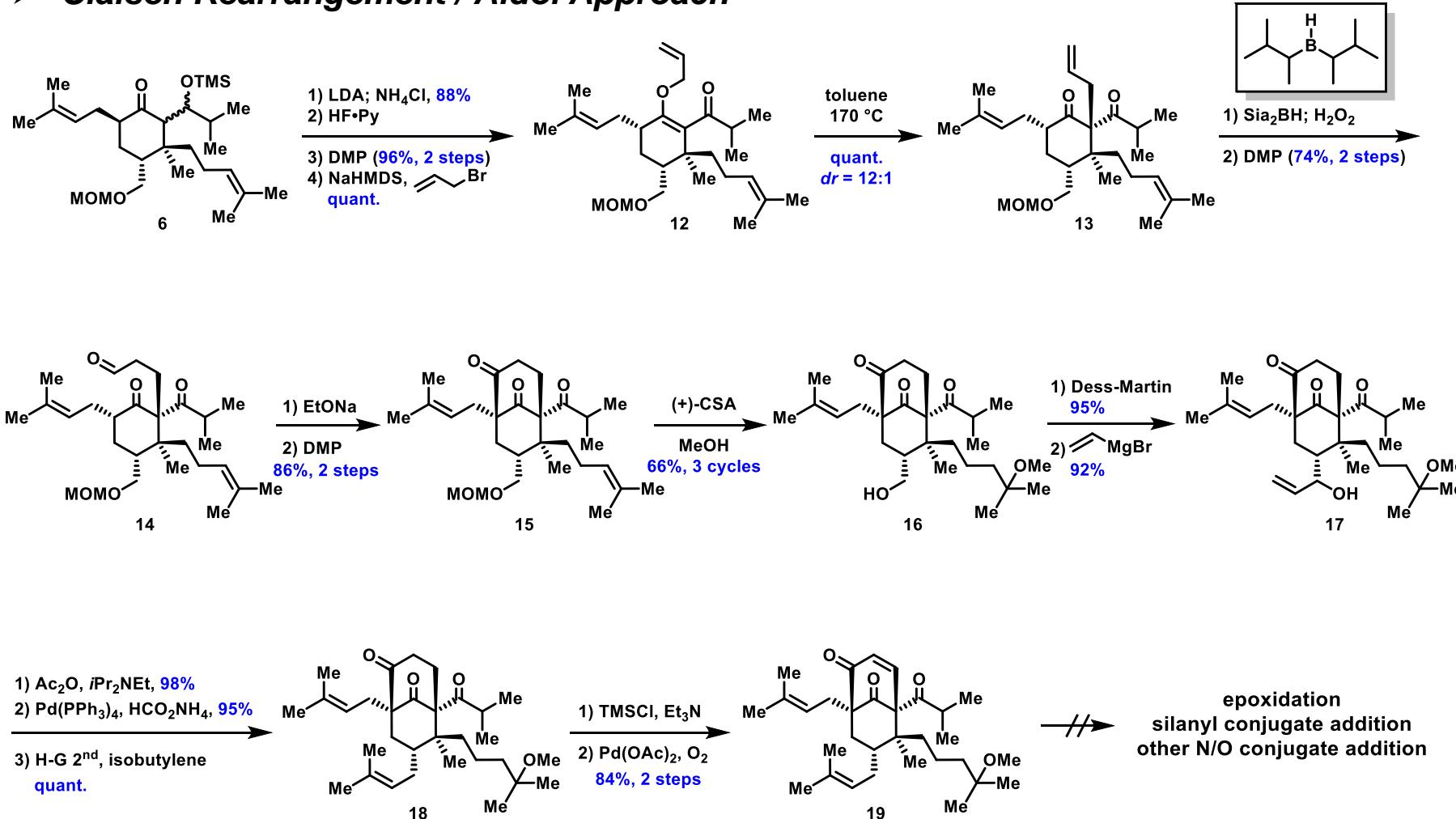
➤ Claisen Rearrangement / RCM Approach



Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103.
Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2010**, *66*, 6569.

Part 4. Shibasaki's Total Synthesis of Hyperforin

➤ Claisen Rearrangement / Aldol Approach

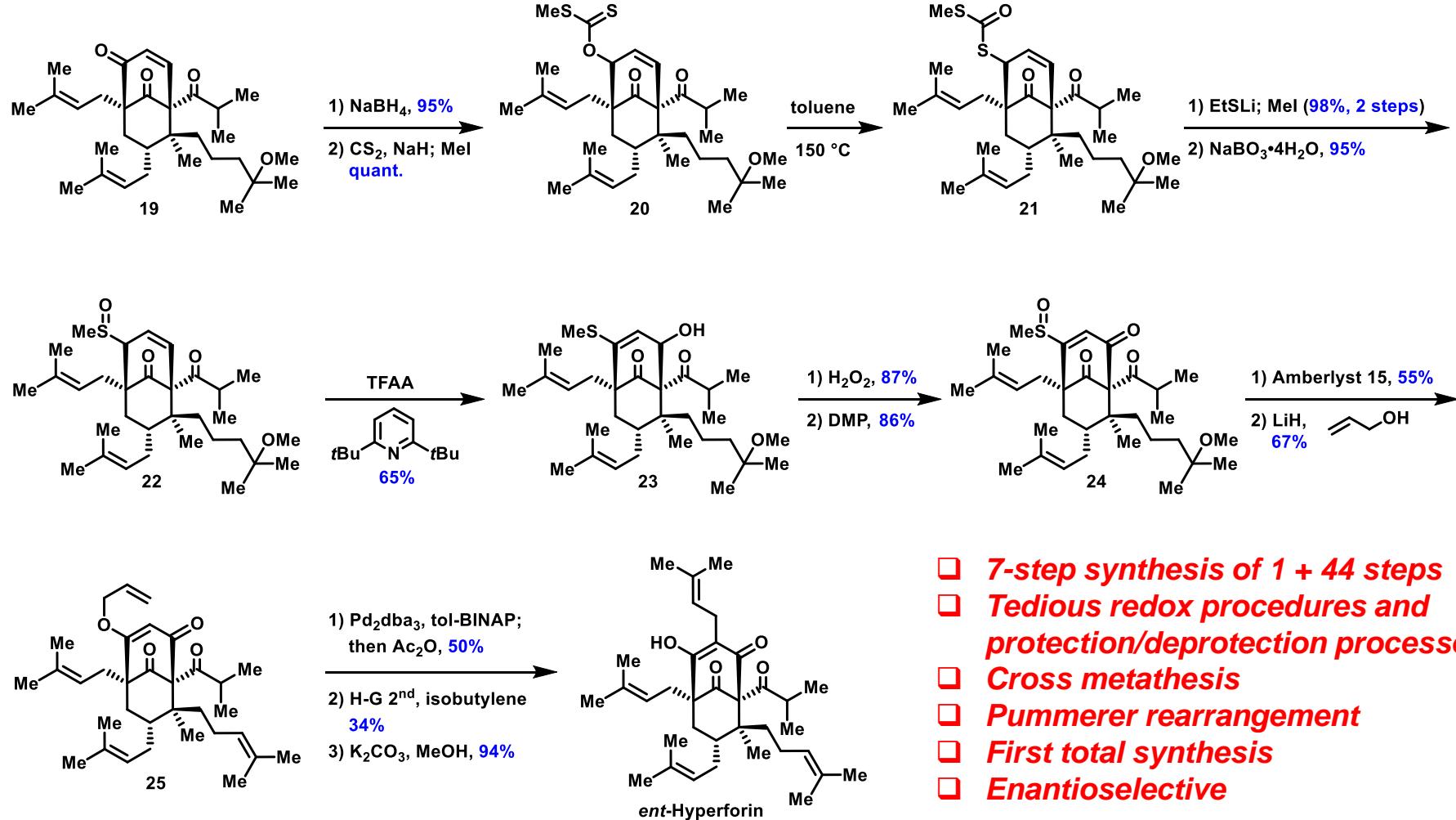


Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, 49, 1103.
Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2010**, 66, 6569.

The Story of Hyperforin

Part 4. Shibasaki's Total Synthesis of Hyperforin

➤ Claisen Rearrangement / Aldol / Pummerer Approach



Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, 49, 1103.
Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2010**, 66, 6569.

Part 5. Nakata's Total Synthesis of Hyperforin

➤ Professor Masahisa Nakata



中田 雅久

Research Interests:

- Total Synthesis
- Synthetic Methodology
- Chemical Biology

Publications:

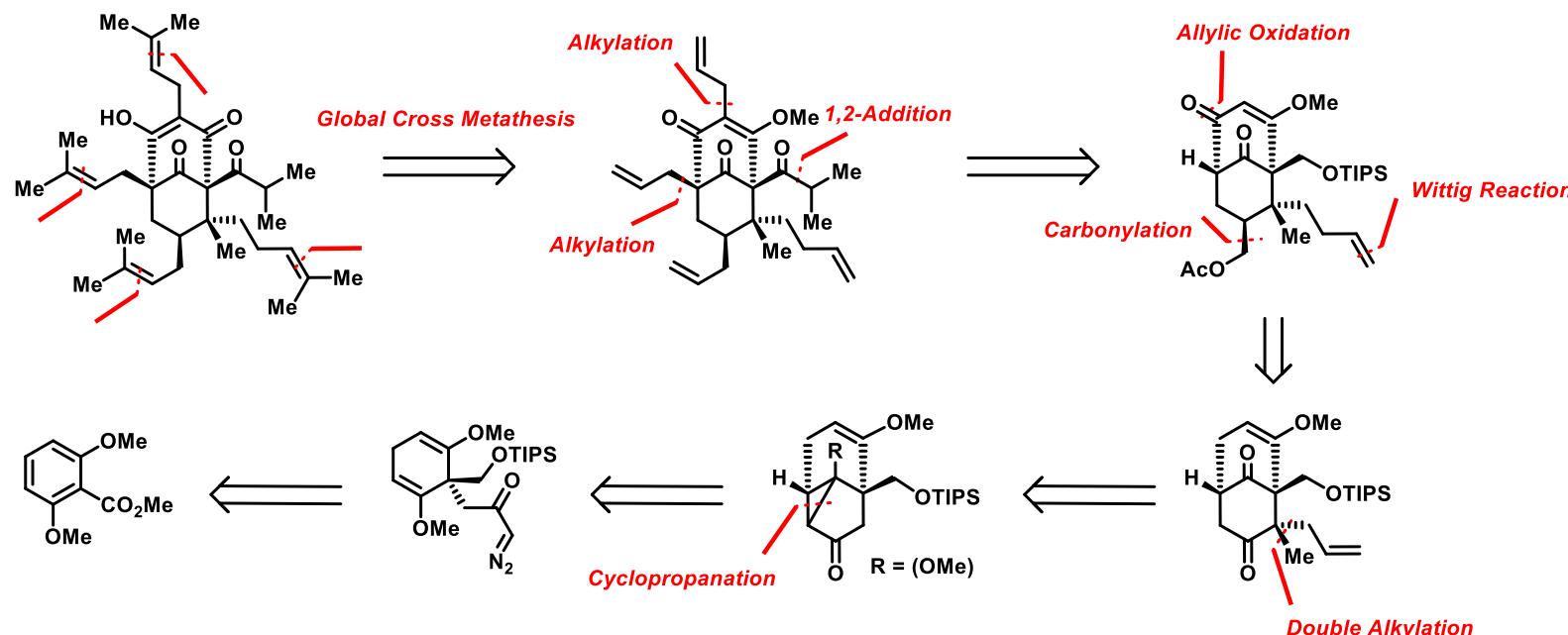
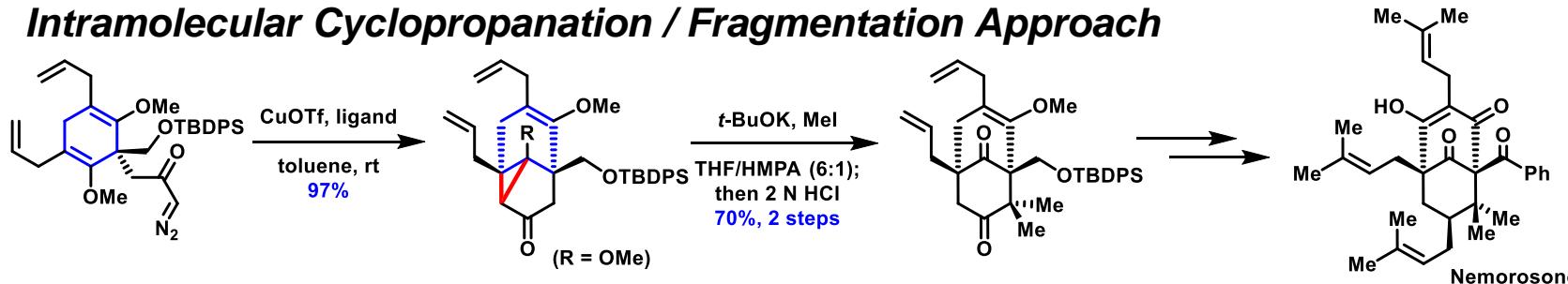
- 144 publications (1988-present)
- 9 JACS, 7 ACIE

Biography:

- 1982: University of Tokyo, **B.S.**
- 1982-1984: University of Tokyo, **M.S.**
- 1984-1988: University of Tokyo, **Assistant Professor, Ph.D.**
Research advisor: Prof. Masaji Ohno
- 1988-1992: University of Tokyo, **Post-doctoral fellow**
Research advisor: Prof. Masakatsu Shibasaki
- 1992-1995: The Scripps Research Institute, **Post-doctoral fellow**
Research advisor: Prof. K. C. Nicolaou
- 1995-2000: Waseda University, **Associate Professor**
- 2000-present: Waseda University, **Professor**

Part 5. Nakata's Total Synthesis of Hyperforin

➤ Intramolecular Cyclopropanation / Fragmentation Approach



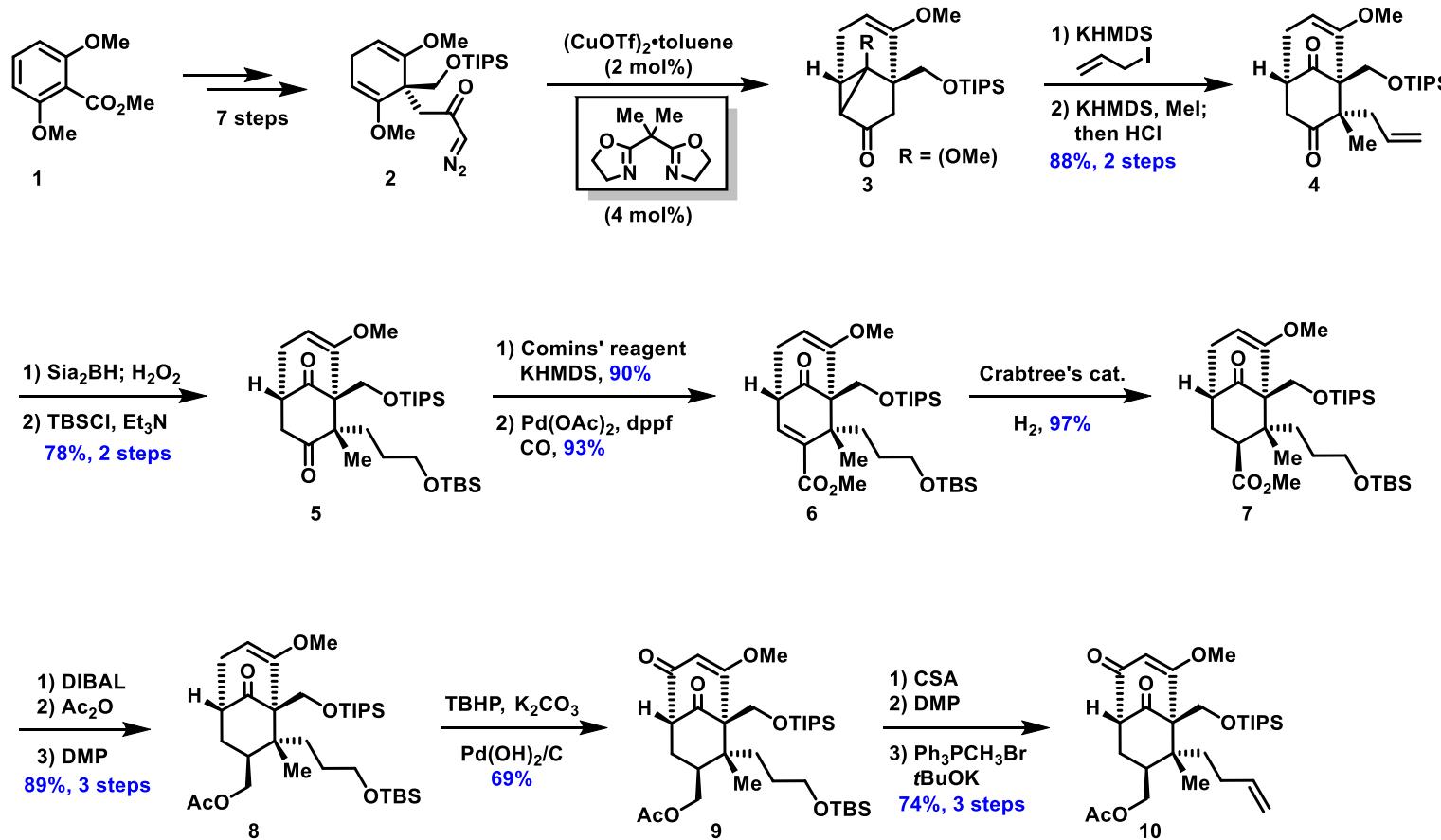
Abe, M.; Saito, A.; Nakata, M. *Tetrahedron Lett.* **2010**, 51, 1298.

Nemorosone: Uwamori, M.; Saito, A.; Abe, M.; Nakata, M. *J. Org. Chem.* **2012**, 77, 5098.

Uwamori, M.; Nakata, M. *Tetrahedron Lett.* **2013**, 54, 2022.

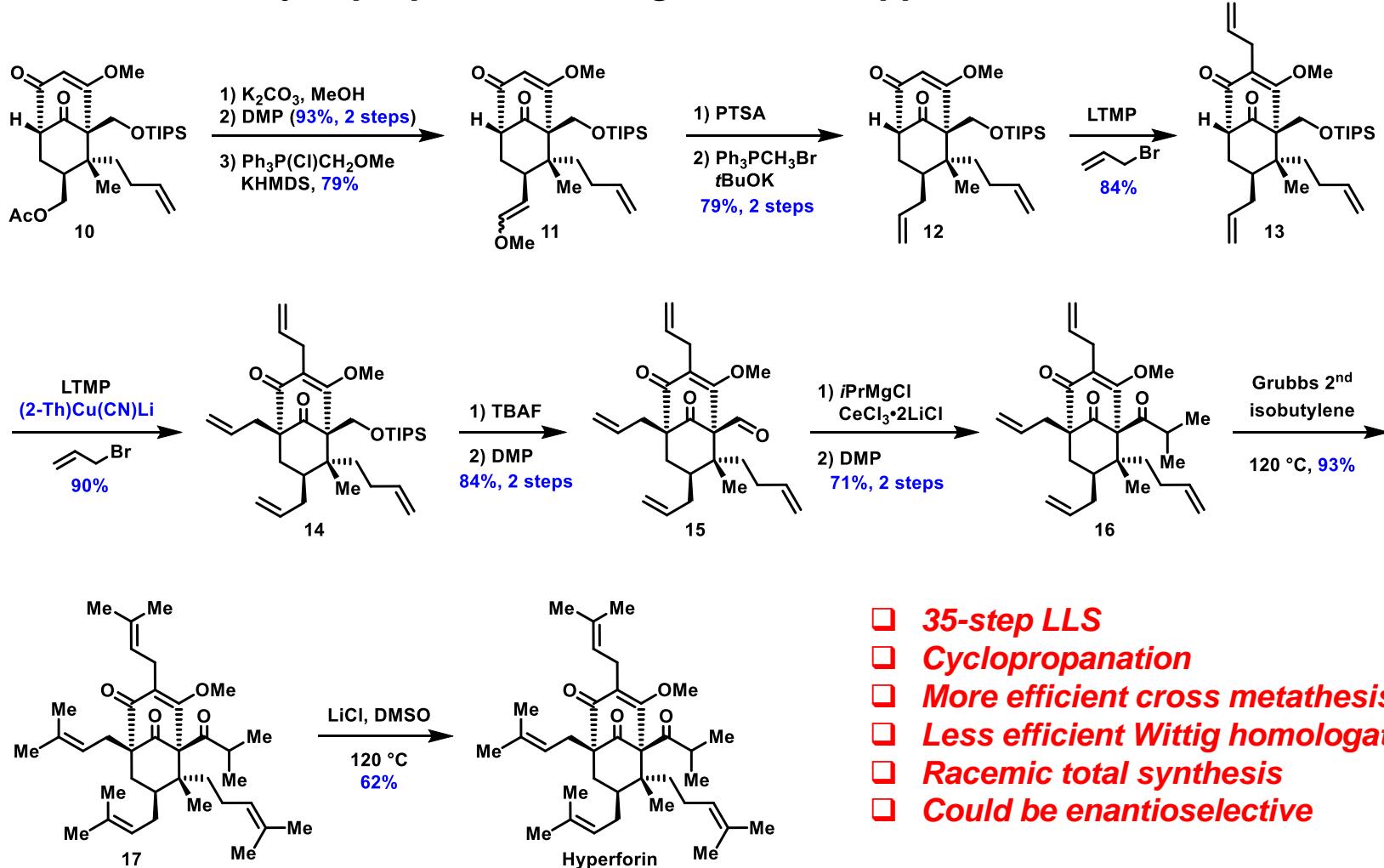
Part 5. Nakata's Total Synthesis of Hyperforin

➤ *Intramolecular Cyclopropanation / Fragmentation Approach*



Part 5. Nakata's Total Synthesis of Hyperforin

➤ *Intramolecular Cyclopropanation / Fragmentation Approach*



Part 6. Shair's Total Synthesis of Hyperforin

➤ Professor Matthew Shair



Biography:

- 1986-1990: University of Rochester, **B.S. with distinction**
- 1990-1993: Yale University, **M.S.**
- 1993-1995: Columbia University, **Ph.D.**
Research advisor: Prof. S. J. Danishefsky
- 1995-1997: Harvard University, **Post-doctoral fellow**
Research advisor: Prof. S. L. Schreiber
- 1997-2001: Harvard University, **Assistant Professor**
- 2001-2002: Harvard University, **Associate Professor**
- 2002-present: Harvard University, **Professor**

Research Interests:

- Cancer Biology
- Chemical Biology
- Total Synthesis

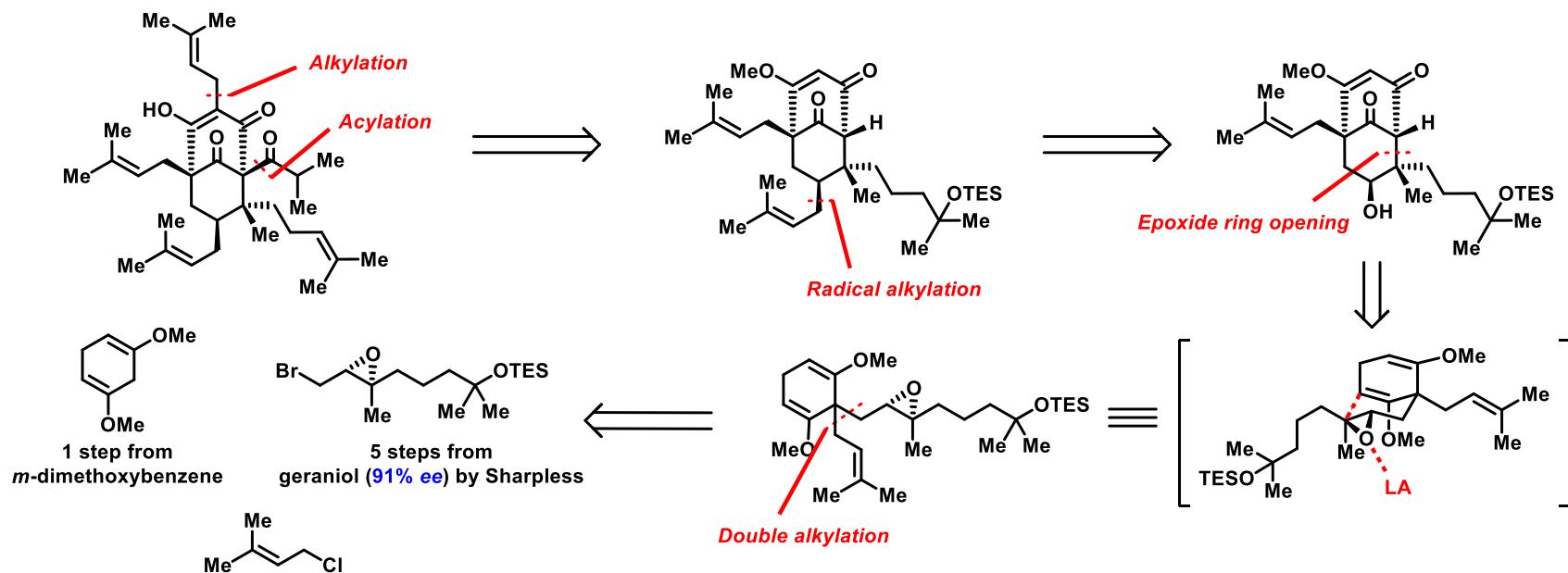
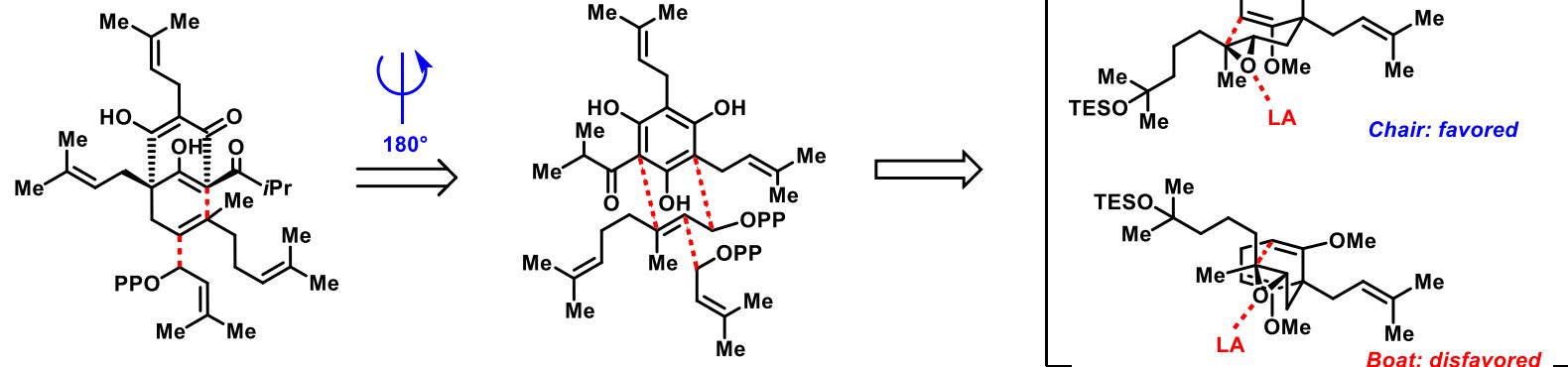
Publications:

- 37 publications (Independent career)
- 1 *Nature*, 18 *JACS*, 3 *ACIE*

The Story of Hyperforin

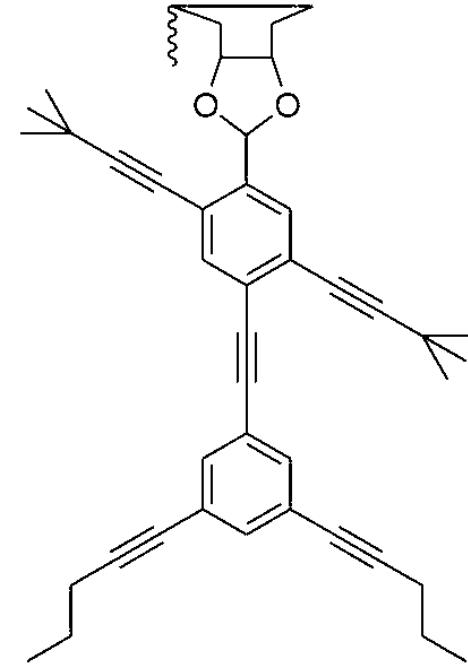
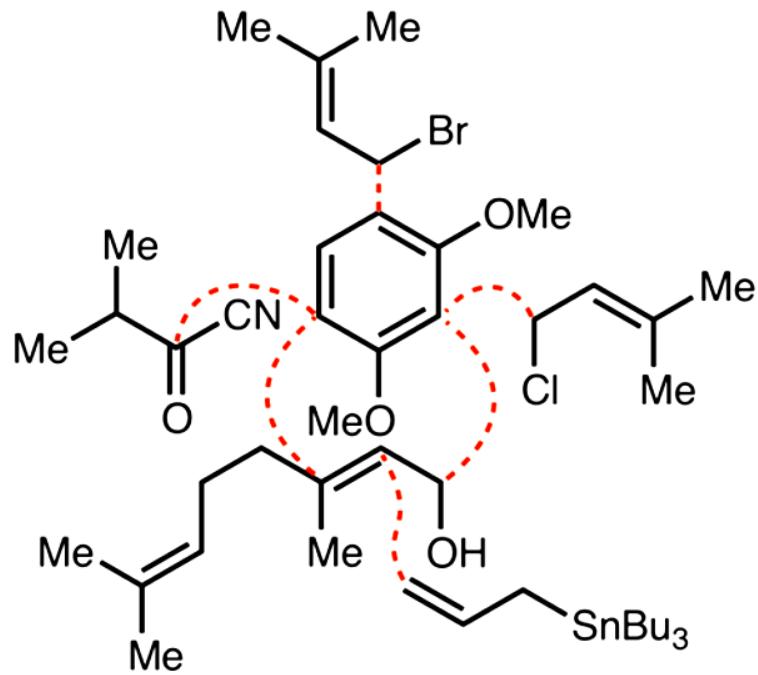
Part 6. Shair's Total Synthesis of Hyperforin

► Biomimetic Cyclization Approach



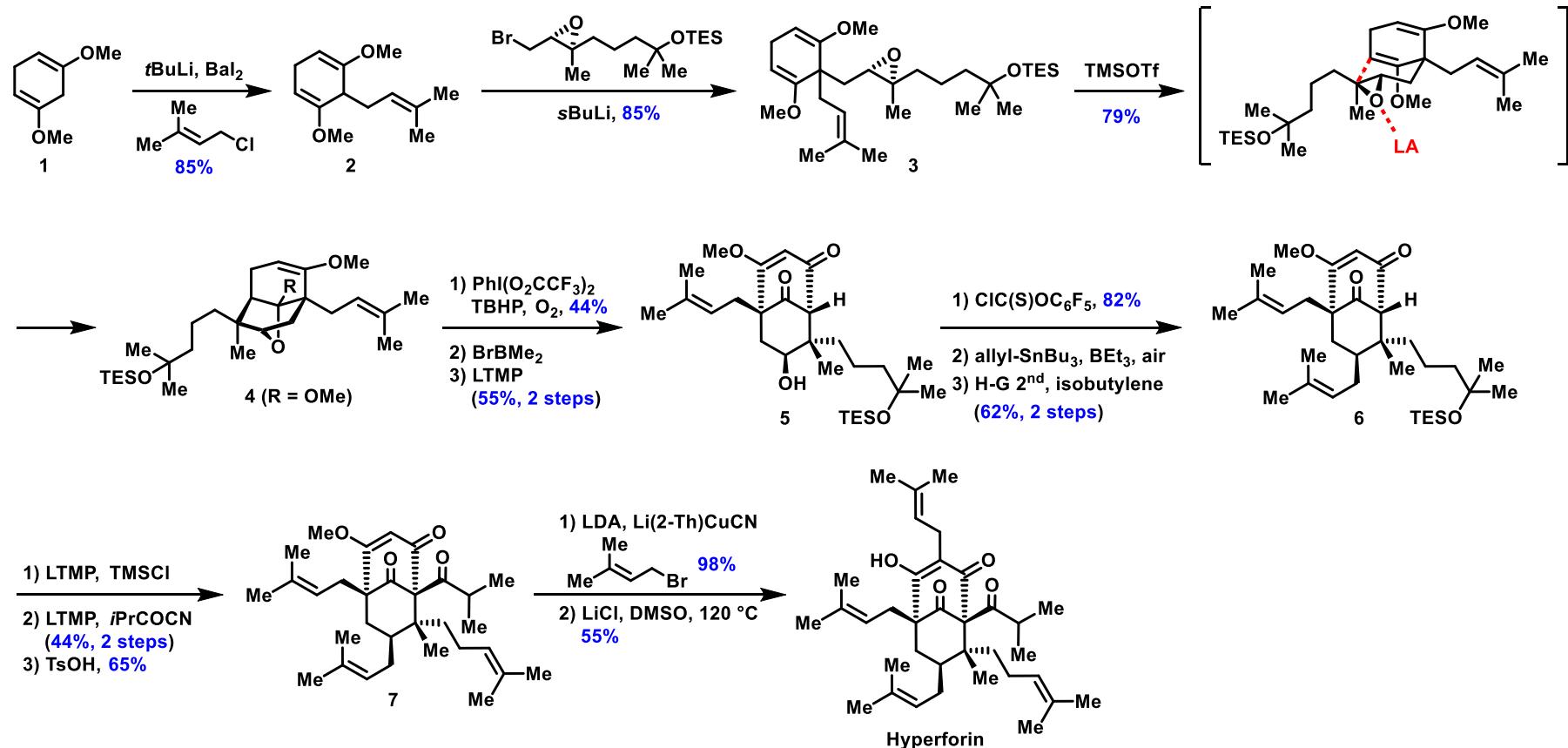
Part 6. Shair's Total Synthesis of Hyperforin

➤ **Biomimetic Cyclization Approach**



Part 6. Shair's Total Synthesis of Hyperforin

➤ Biomimetic Cyclization Approach



- 18-step LLS
- Efficient Biomimetic Cyclization
- Enantioselective

Part 7. Barriault's Total Synthesis of Hyperforin

➤ Professor Louis Barriault



Biography:

- 1993: University of Sherbrooke, **B.S.**
- 1993-1997: University of Sherbrooke, **Ph.D.**
Research advisor: Prof. Pierre Deslongchamps
- 1997-1999: Ohio State University, **Post-doctoral fellow**
Research advisor: Prof. L. A. Paquette
- 1999-2010: University of Ottawa, **Assistant Professor**
- 2010-present: University of Ottawa, **Full Professor**

Research Interests:

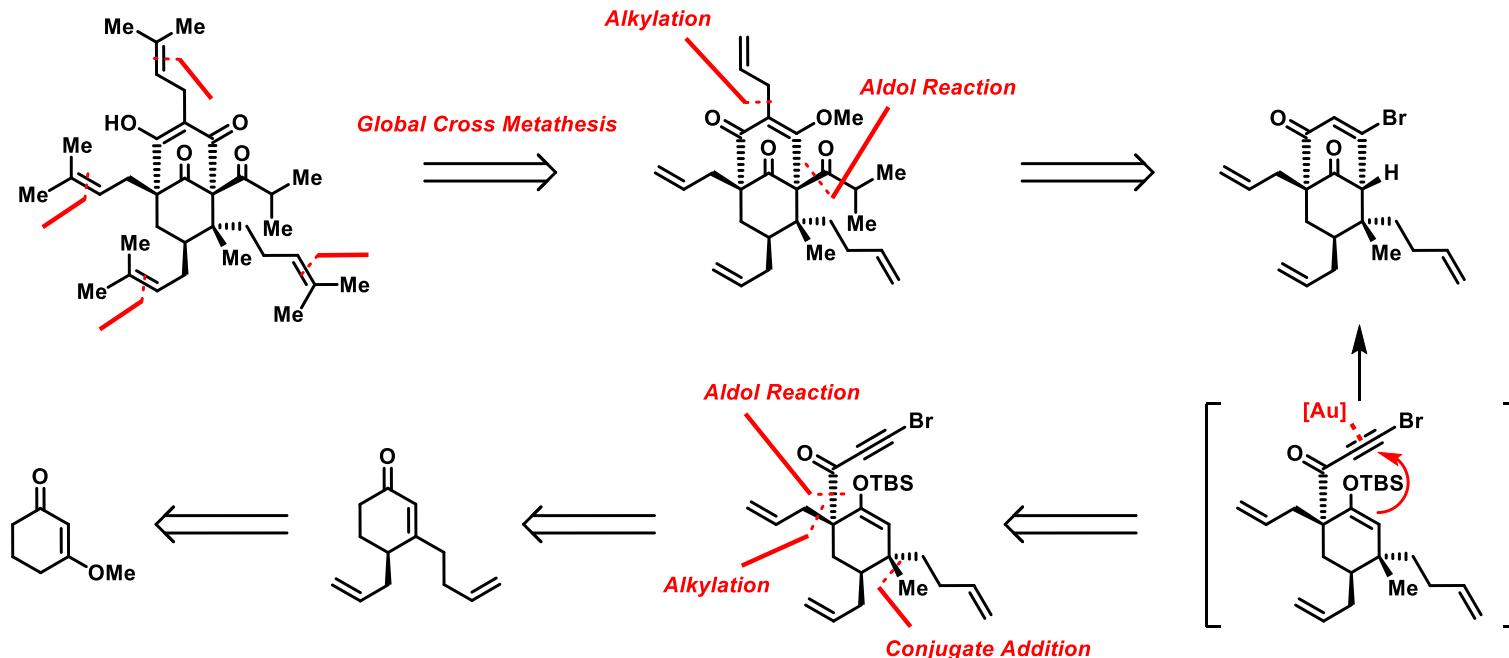
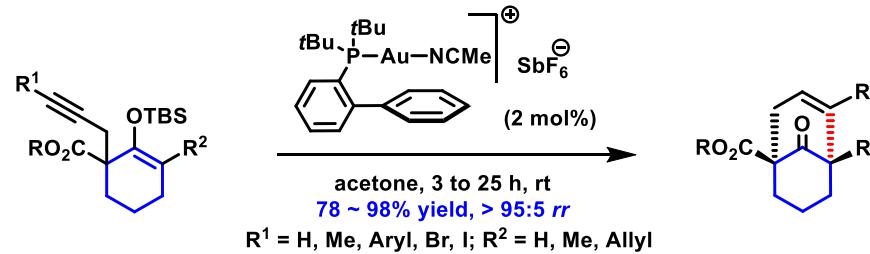
- Gold Catalysis
- Total Synthesis

Publications:

- 50 publications (1997-present)
- 1 *Nature*, 3 *JACS*, 4 *ACIE*

Part 7. Barriault's Total Synthesis of Hyperforin

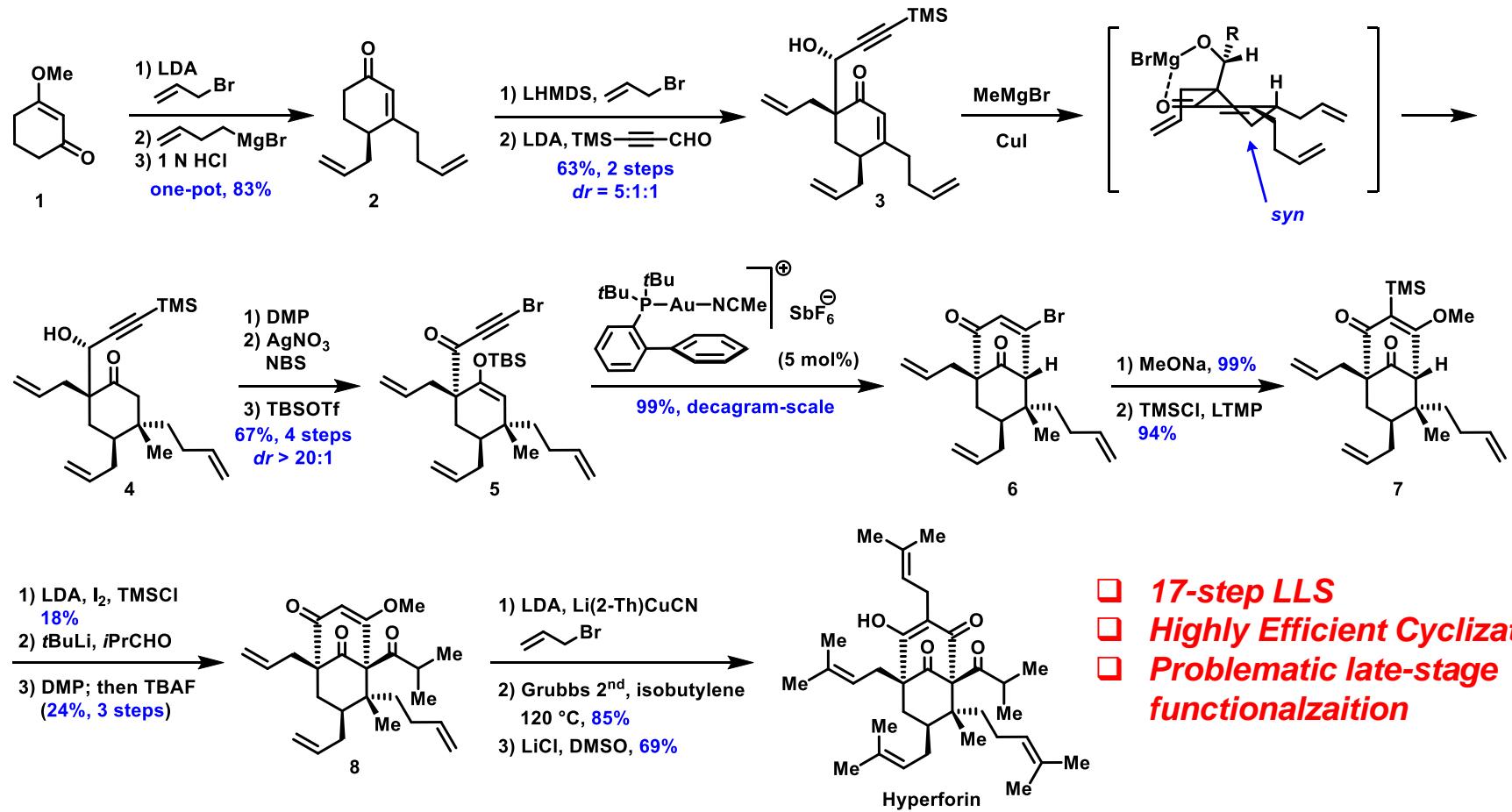
➤ Au-Catalyzed Cyclization Approach



Mitasev, B.; Be'tournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, 11, 4236.
Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, 53, 6701.

Part 7. Barriault's Total Synthesis of Hyperforin

➤ Au-Catalyzed Cyclization Approach



Part 8. Maimone's Total Synthesis of Hyperforin

➤ Professor Thomas Maimone



Biography:

- 2000-2004: University of California, Berkeley, B.S.
Research advisor: Prof. Dirk Trauner
- 2004-2009: The Scripps Research Institute, Ph.D.
Research advisor: Prof. P. S. Baran
- 2009-2012: MIT, NIH Post-doctoral fellow
Research advisor: Prof. S. L. Buchwald
- 2012-present: University of California, Berkeley
Assistant Professor

Research Interests:

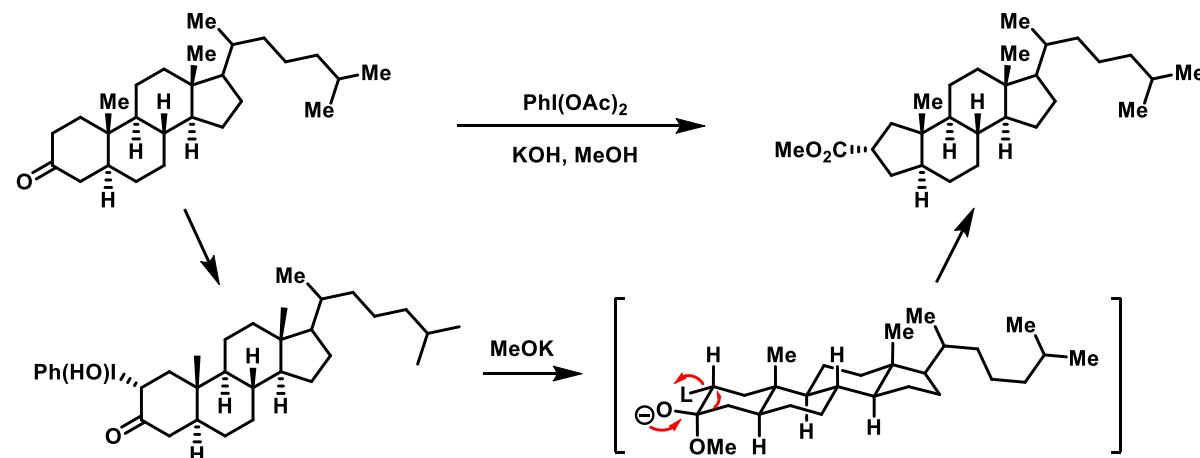
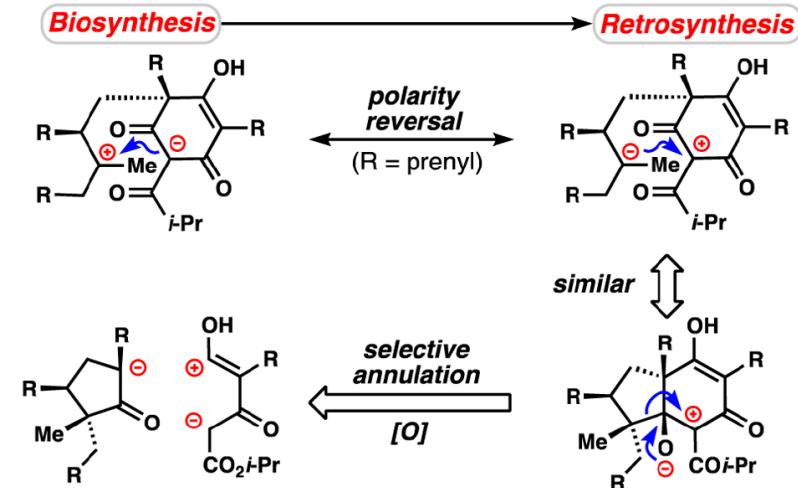
- Total Synthesis

Publications:

- 17 publications (2000-present)
- 2 *Nature*, 8 *JACS*, 4 *ACIE*
- 4 publications (Independent career)
- 2 *JACS*, 2 *ACIE*

Part 8. Maimone's Total Synthesis of Hyperforin

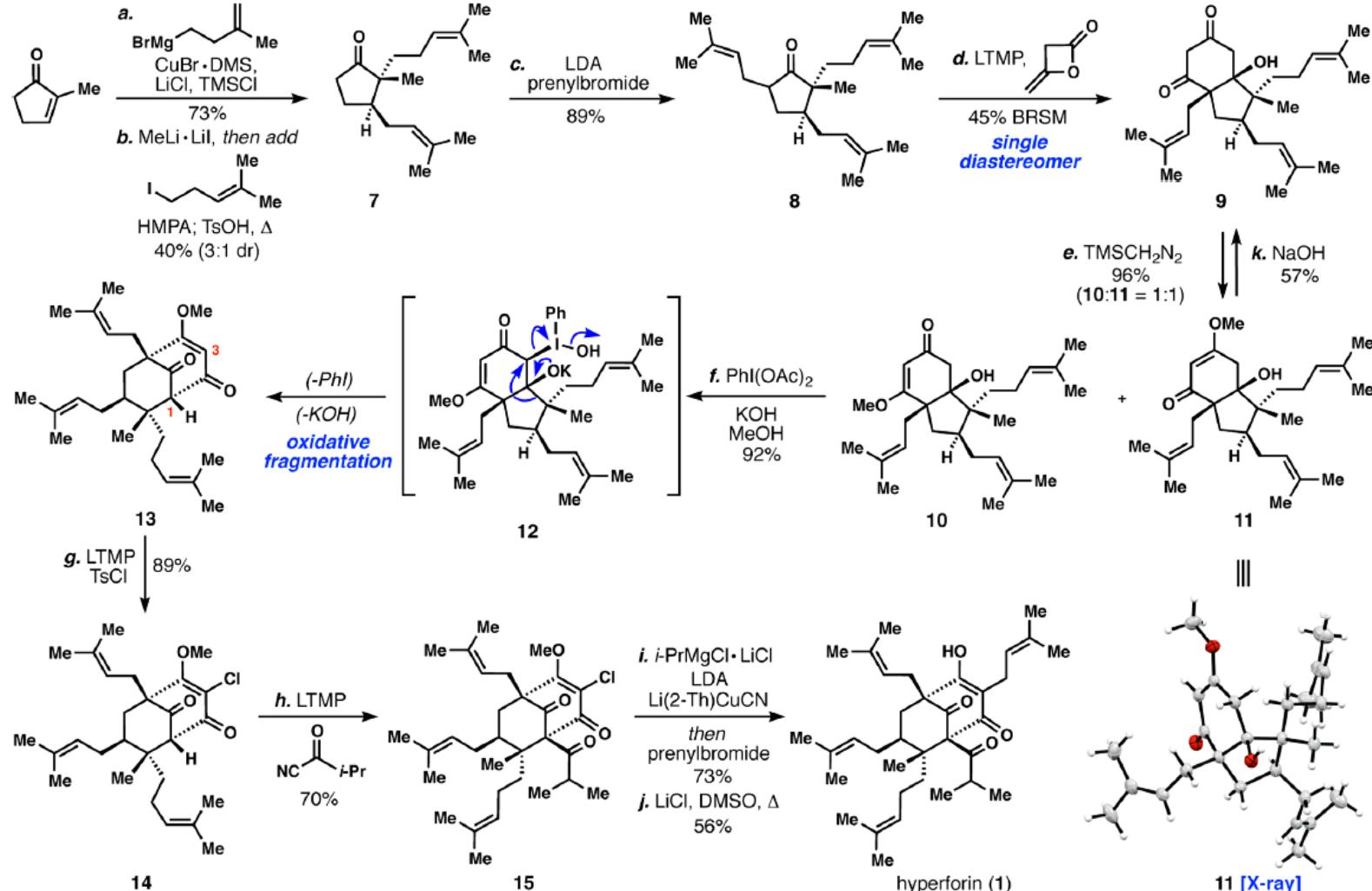
➤ Polarity-reverse C-C Bond Formation Approach



Daum, S. J. *Tetrahedron Lett.* 1984, 25, 4725.
Ting, C. P.; Maimone, T. J. *J. Am. Chem. Soc.* 2015, 137, 10516.

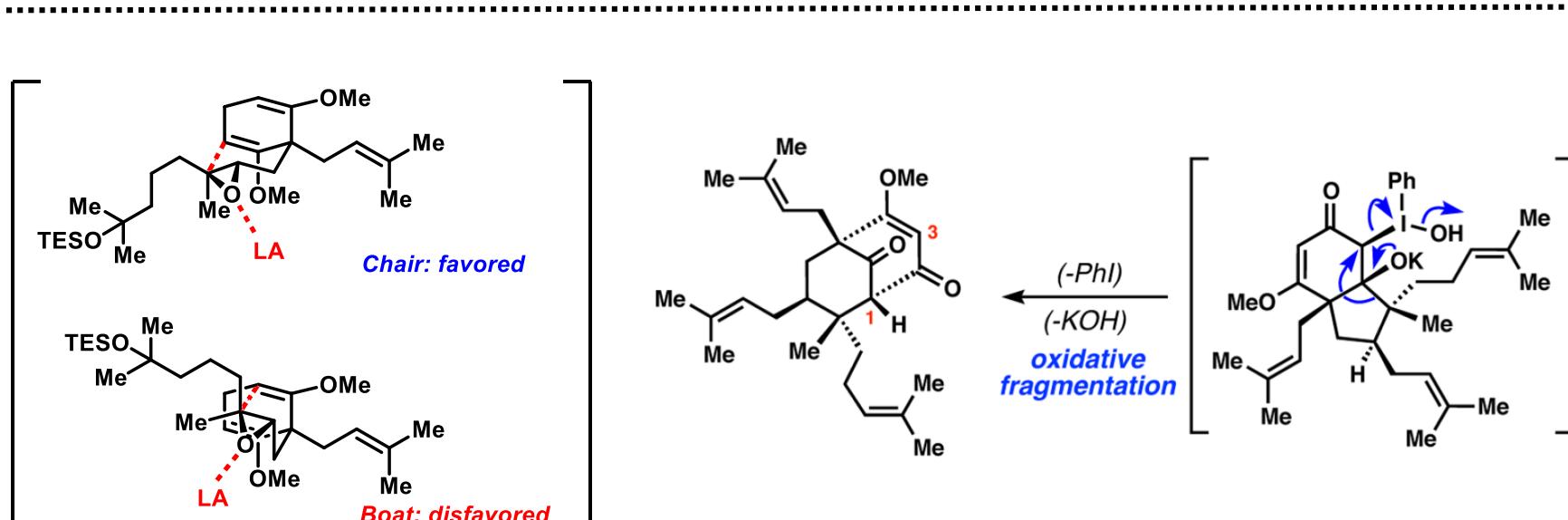
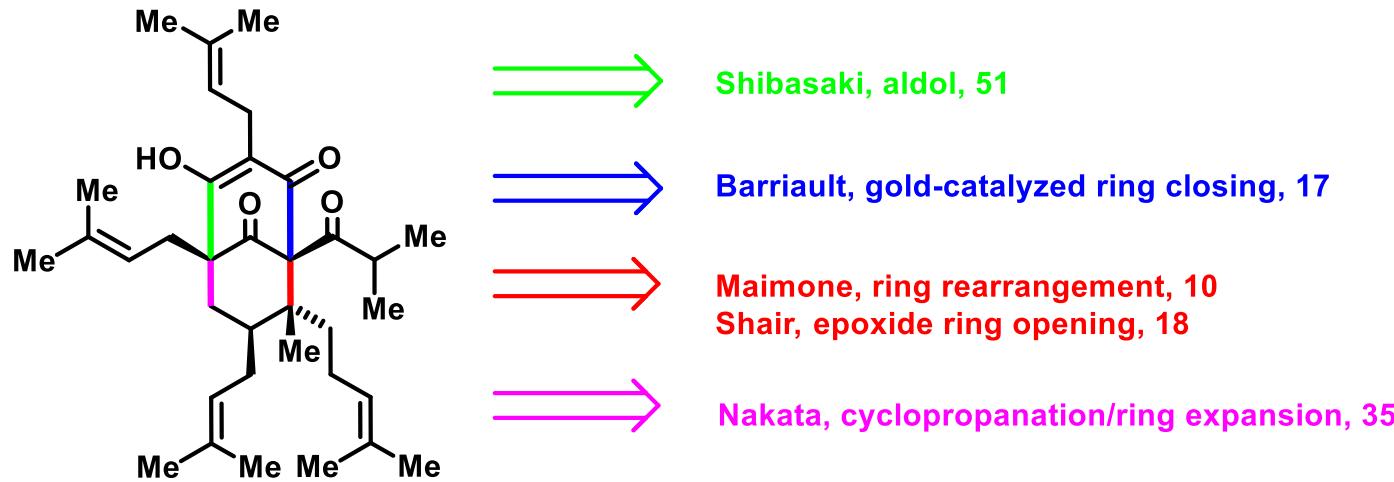
Part 8. Maimone's Total Synthesis of Hyperforin

➤ **Polarity-reverse C-C Bond Formation Approach** **10-step LLS**



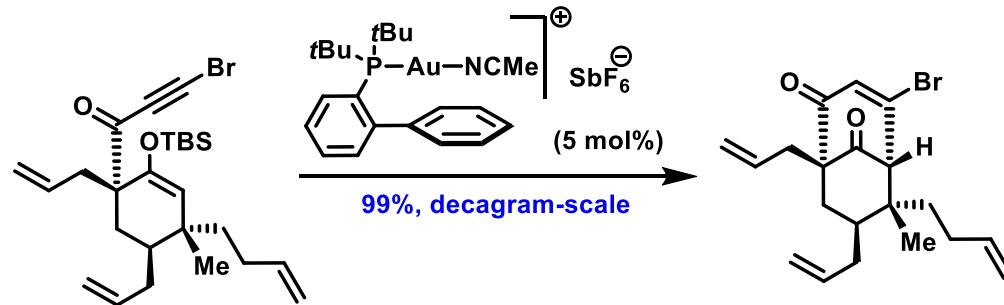
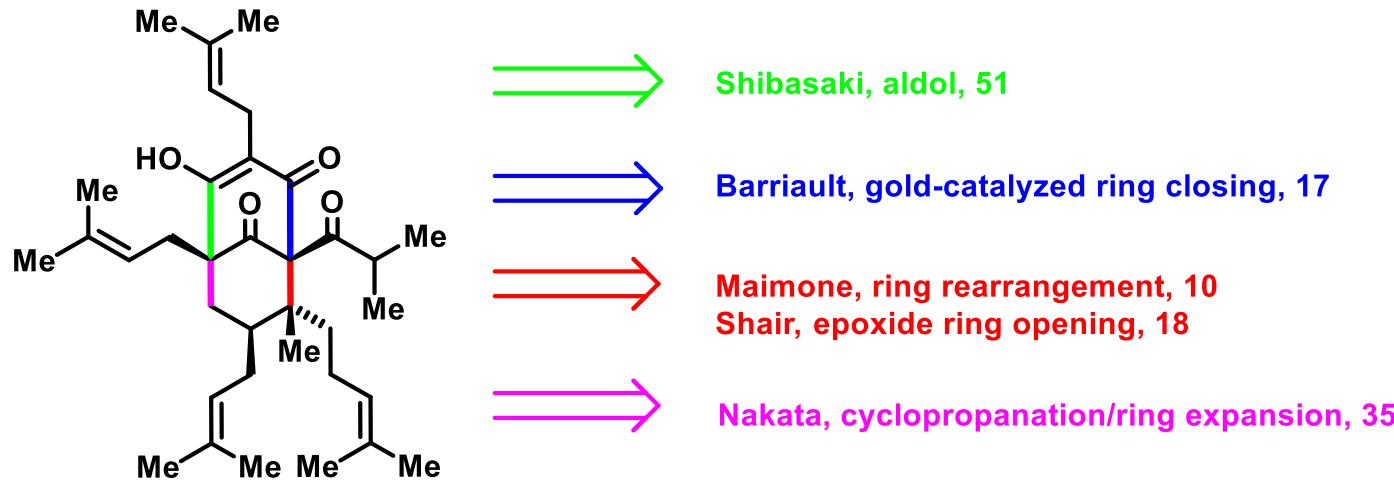
The Story of Hyperforin

Summary



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Summary



The Story of Hyperforin



Thank you for your attention!