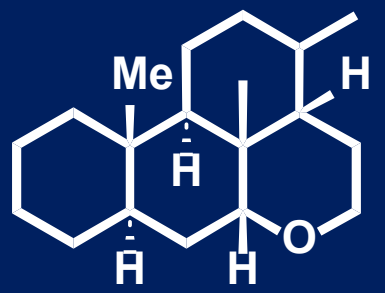
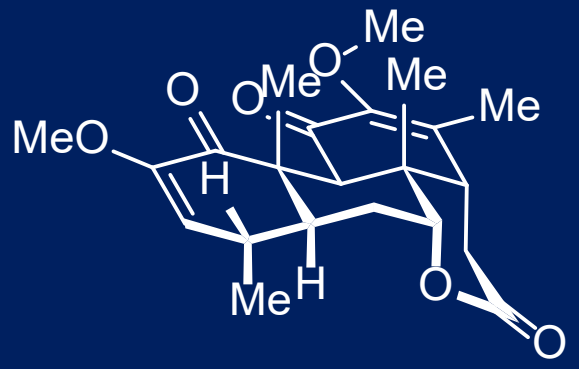
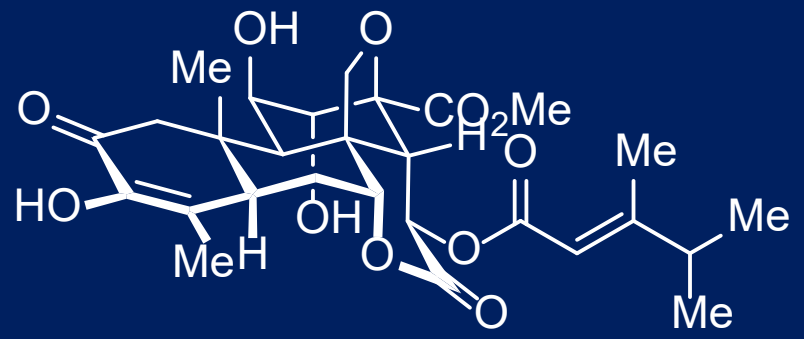



**quassin**




**bruceantin**

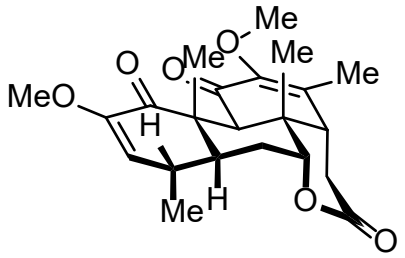
# Synthetic Studies of Quassinoids

Reporter: Xia, Tianrun
Supervisor: Prof. Luo, Tuoping
College of Chemistry and Molecular Engineering @ PKU
June, 15th, 2024

# Outline

- Introduction – Phytochemistry and Basic structures
- Synthetic studies toward quassin
  - Preliminary investigations
  - Total synthesis of quassin
- Total synthesis of other quassinoids
- Synthetic studies of core structure of quassinoids
- Summary

# Introduction of Quassinoids

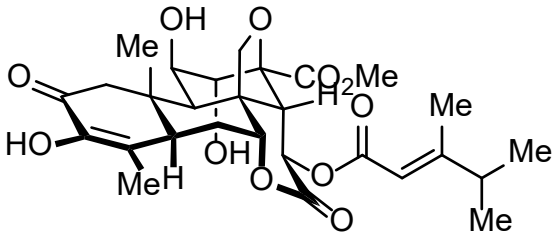



**quassin**

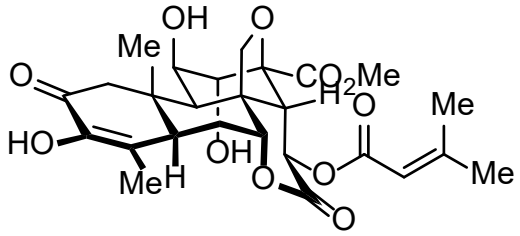
- 1937, quassin and neoquassin
- Extracts from plants of Simaroubaceae family
- Traditional folk medicines in Ethiopia and Asia
- Anti-tumor, anti-viral, anti-malarial, anti-ulcer, and anti-inflammatory activities
- Class of inhibitor for eukaryotic protein synthesis. Interfere at the peptidyl-transferase site to terminate elongation
- Phosphorylation; membrane polarization; regulate DNA and RNA synthesis

G. Fiaschetti, M. A. Grotzer, T. Shalaby, D. Castelletti and A. Arcaro*. *Curr. Med. Chem.*, **2011**, *18*, 316-328.
Polonsky, J. Quassinoid Bitter Principles. Fortschr. *Chem. Org. Naturst.*, **1973**, *30*, 101-50.

# Phytochemistry




**bruceantin**




**brusatol**

- Bruceantin: 1974, Brucea antidysenterica (2 g/10 kg, 0.02%)
- Phase II: breast cancer and malignant melanoma; failed due to toxicity (hypotension, nausea, vomiting and fever) and poor efficacy
- induced apoptosis in leukemia cells (2004): 2.5-5 mg/kg *in vivo.*
- Brusatol: Most potent inducer of cellular differentiation


S. Morris Kupchan*, Ronald W. Britton, John A. Lacadie, Myra F. Ziegler, and Carl W. Sigel. *J. Org. Chem.* **1975**, *40*, 5, 648–654.

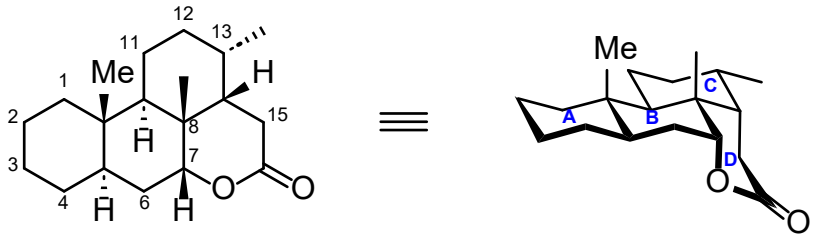
Beutler, J. A.; Kang, M. I.; Robert, F.; Clement, J. A.; Pelletier, J.; Colburn, N. H.; McKee, T. C.; Goncharova, E.; McMahon, J. B.; Henrich, C. J. *J. Nat. Prod.*, **2009**, 72, 3, 503-506.

Wiseman, C. L.; Yap, H. Y.; Bedikian, A. Y.; Bodey, G. P.; Blumenschein, G. R. *Am. J. Clin. Oncol.*, **1982**, *5*, 4, 389-91.

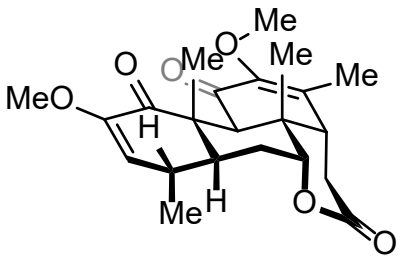
Arseneau, J. C.; Wolter, J. M.; Kuperminc, M.; Ruckdeschel, J. C. *Invest. New Drugs*, **1983**, *1*, 3, 239-42.

Cuendet, M.; Christov, K.; Lantvit, D. D.; Deng, Y.; Hedayat, S.; Helson, L.; McChesney, J. D.; Pezzuto, *J. M. Clin. Cancer Res.*, **2004**, *10*, 3, 1170-9.

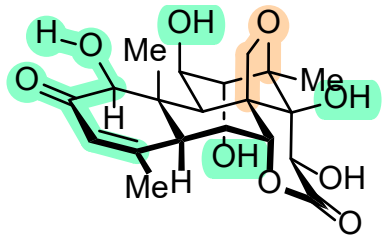
# Structural-activity Relationship



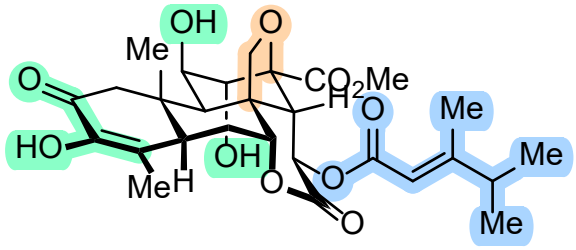
- nortriterpenoids. C18, C19, C20, C22, C25
- 4-ring skeleton
- *α,β*-unsaturated ketone and the *α*-hydroxyl group
- ether bridge on C-ring
- ester side chain
- C1, C3, C11, C12 free hydroxyl group (due to glycosylation)



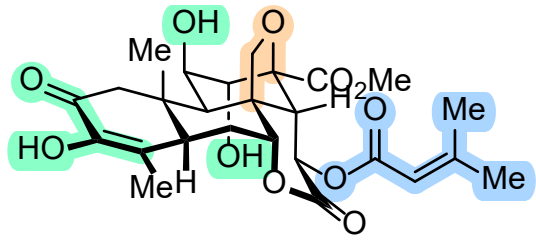
**quassin**



**brucein**



**bruceantin**



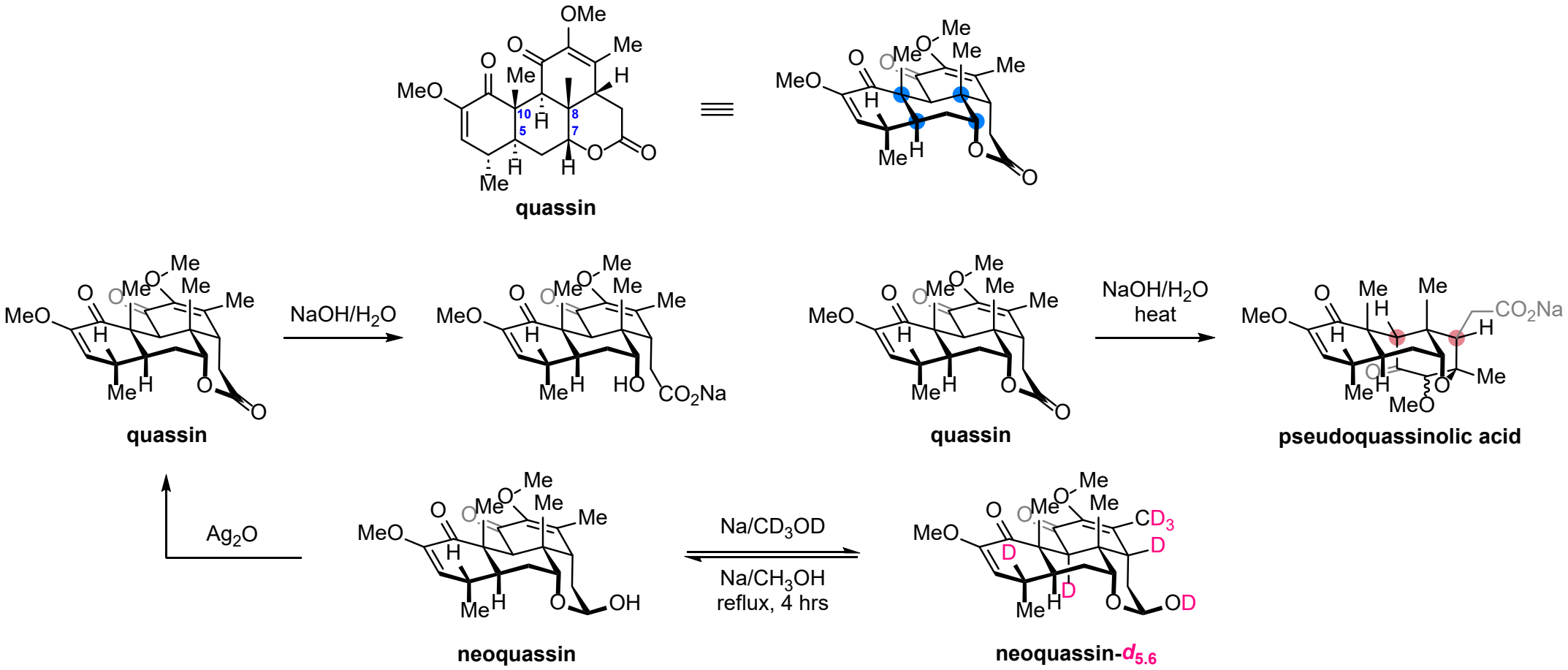
**brusatol**


Guo, Z.; Vangapandu, S.; Sindelar, R. W.; Walker, L. A.; Sindelar, R. D. *Curr. Med. Chem.*, **2005**, *12*, 2, 173-190.
Kupchan, S. M.; Britton, R. W.; Lacadie, J. A.; Ziegler, M. F.; Sigel, C. W. *J. Org. Chem.*, **1975**, *40*, 5, 648-654.
Grieco, P. A.; Speake, J. D. *J. Org. Chem.*, **1998**, *63*, 17, 5929-5936.

# Outline

- Introduction – Phytochemistry and Basic structures
- Synthetic studies toward quassin
  - Preliminary investigations
  - Total synthesis of quassin
- Total synthesis of other quassinoids
- Synthetic studies of core structure of quassinoids
- Summary

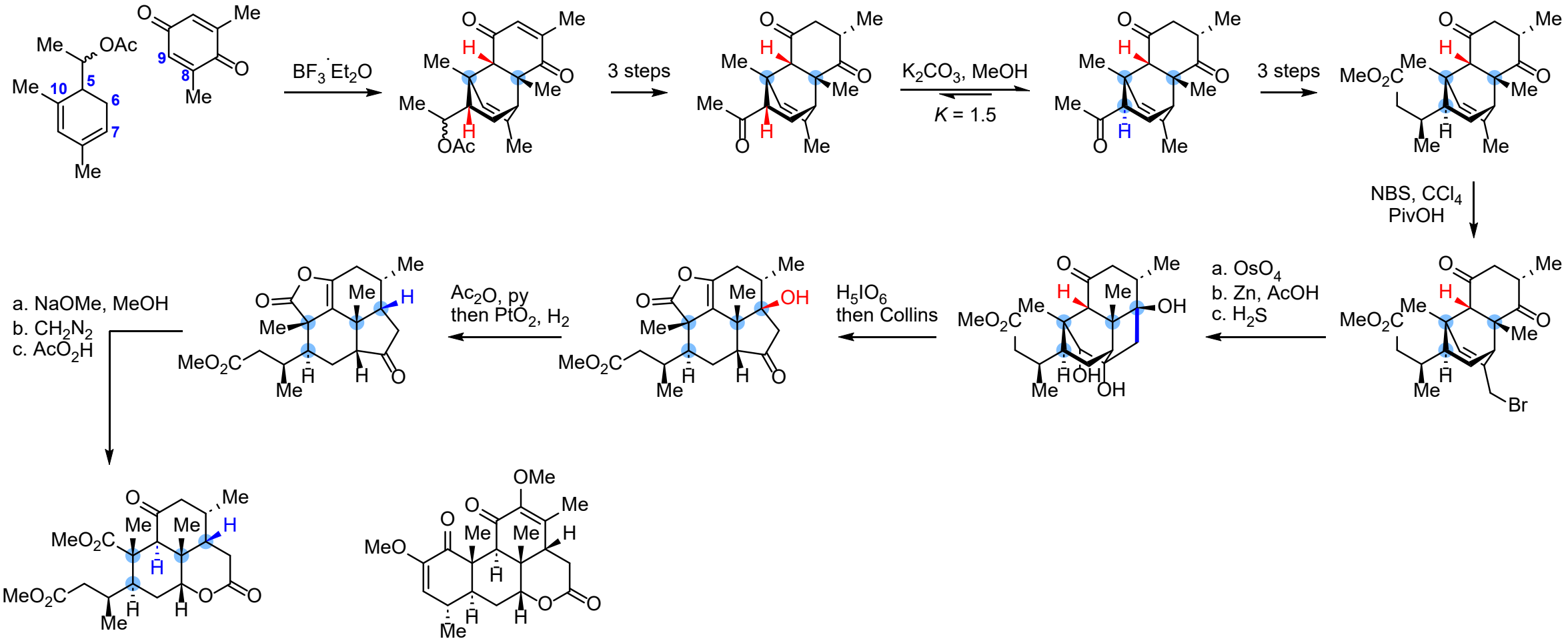
# Chemical Properties of Quassin





Hanson, K. R.; Jaquiss, D. B.; Lamberton, J. A.; Robertson, A. ; Savige, W. E. *J. Chem. Soc.,* **1954**, 4238.
Beer, R. J. S.; Hanson, K. R.; Robertson, A. *J. Chem. Soc.,* **1956**, 3280.
Beer, R. J. S.; Dutton, B. J.; Jaquiss, D. B. ; Robertson, A.; Savige, W. E. *J. Chem. Soc.,* **1956**, 4850
Valenta, Z.; Papadopoulos, S.; Podesva, C. *Tetrahedron,* **1961**, *15*, 100.
Valenta, Z.; Gray, A. H.; Orr, D. E.; Papadopoulos, S.; Podesva, C. *Tetrahedron,* **1962**, *18*, 1433.

# Pioneering Design (Valenta, 1975, 1979)

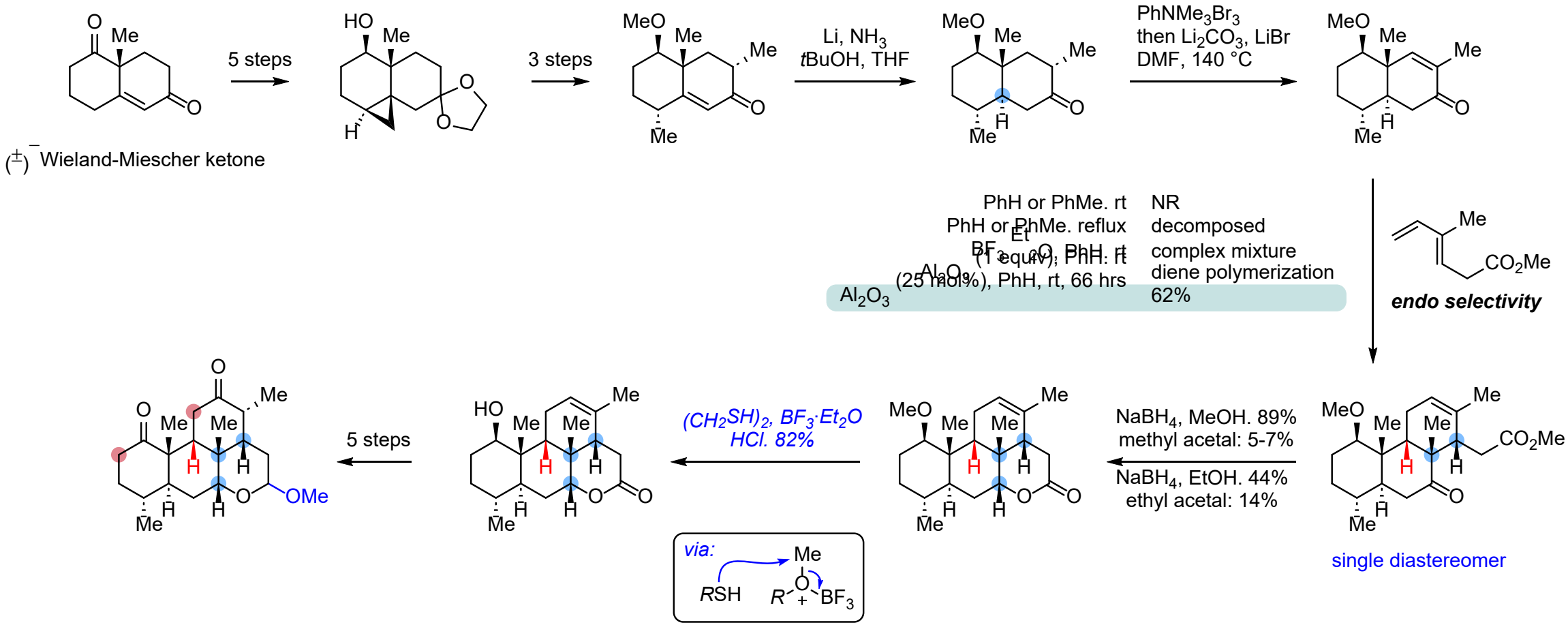



N. Stojanac, A. Sood, Z. Sojanac and Z. Valenta*, *Can. J. Chem.*, **1975**, *53*, 619
N. Stojanac, Z. Sojanac, P. S. White and Z. Valenta*, *Can. J. Chem.*, **1979**, *57*, 3346

# Outline

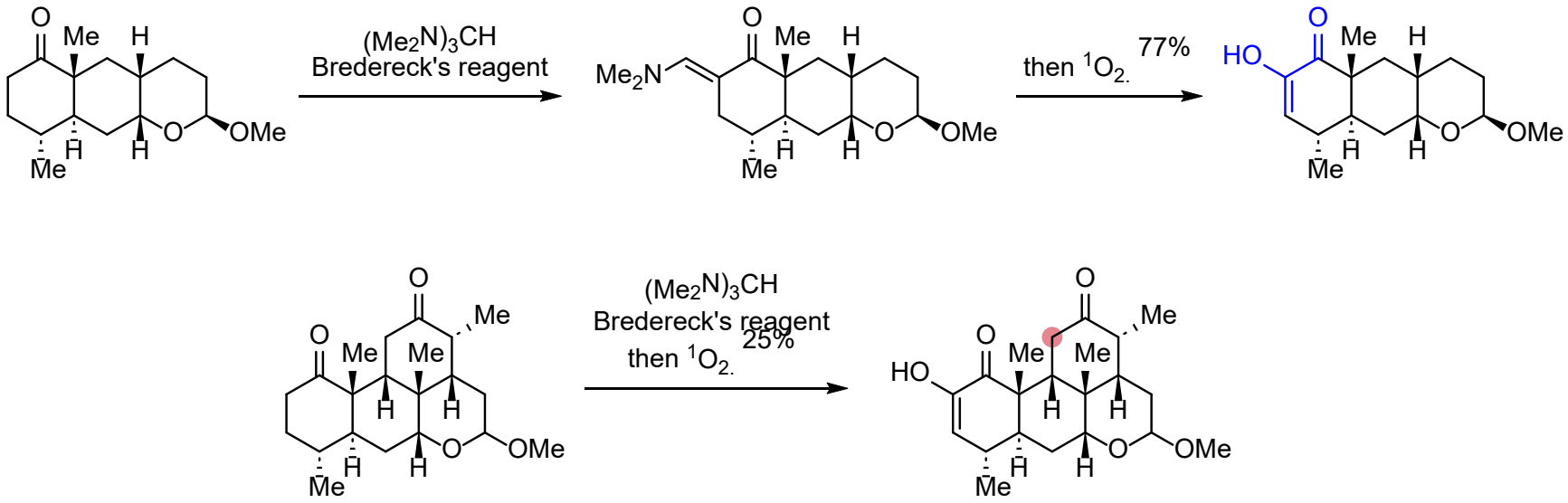
- Introduction – Phytochemistry and Basic structures
- Synthetic studies toward quassin
  - Preliminary investigations
  - Total synthesis of quassin
- Total synthesis of other quassinoids
- Synthetic studies of core structure of quassinoids
- Summary

# The First Racemic Total Synthesis of Quassin (Grieco,1984)




Node, M.; Hori, H.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1.* **1976**, 2237.
Vidari, G.; Ferrino, S.; Grieco, P. A. *J. Am. Chem. Soc.,* **1984**, *106*, 3539

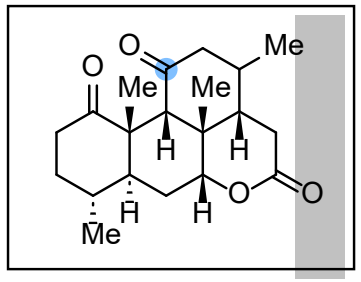
# Initial Attempts to Transfer Diketone to Bis(diosphenol)

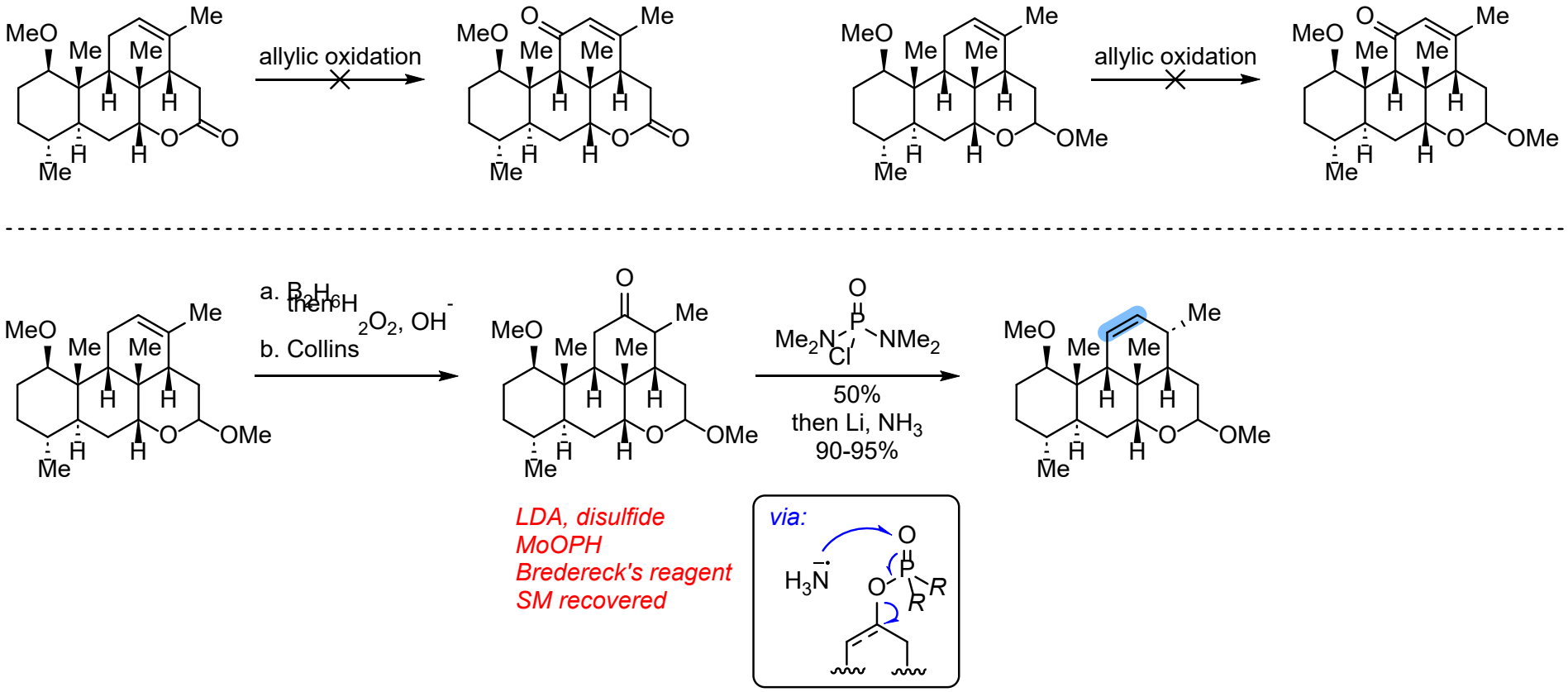




Vidari, G.; Ferrino, S.; Grieco, P. A. *J. Am. Chem. Soc.,* **1984**, *106*, 3539
Wasserman, . H.; Ives, J. L. *J. Org. Chem.* **1978**, *43*, 3238;
Wasserman, . H.; Ives, J. L. *J. Am. Chem. Soc.,* **1976**, *98*, 7868.

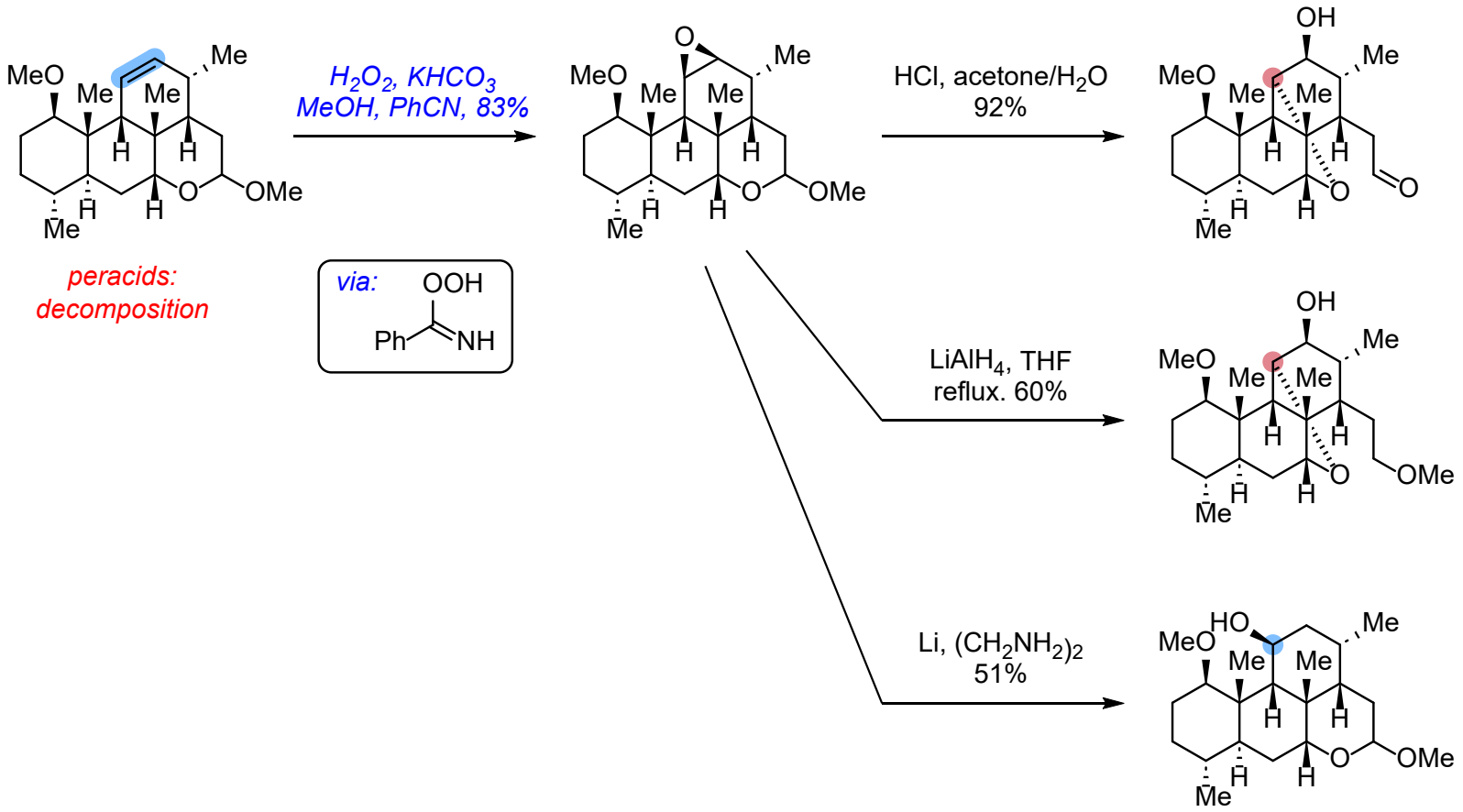
# Manipulations by C12 to introduce Oxygen at C11






Cf.: Ireland, R. E.; Muchmore, D. C; Hengartner, U. *J. Am. Chem. Soc.*, **1972**, *94*, 5098
Vidari, G.; Ferrino, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539

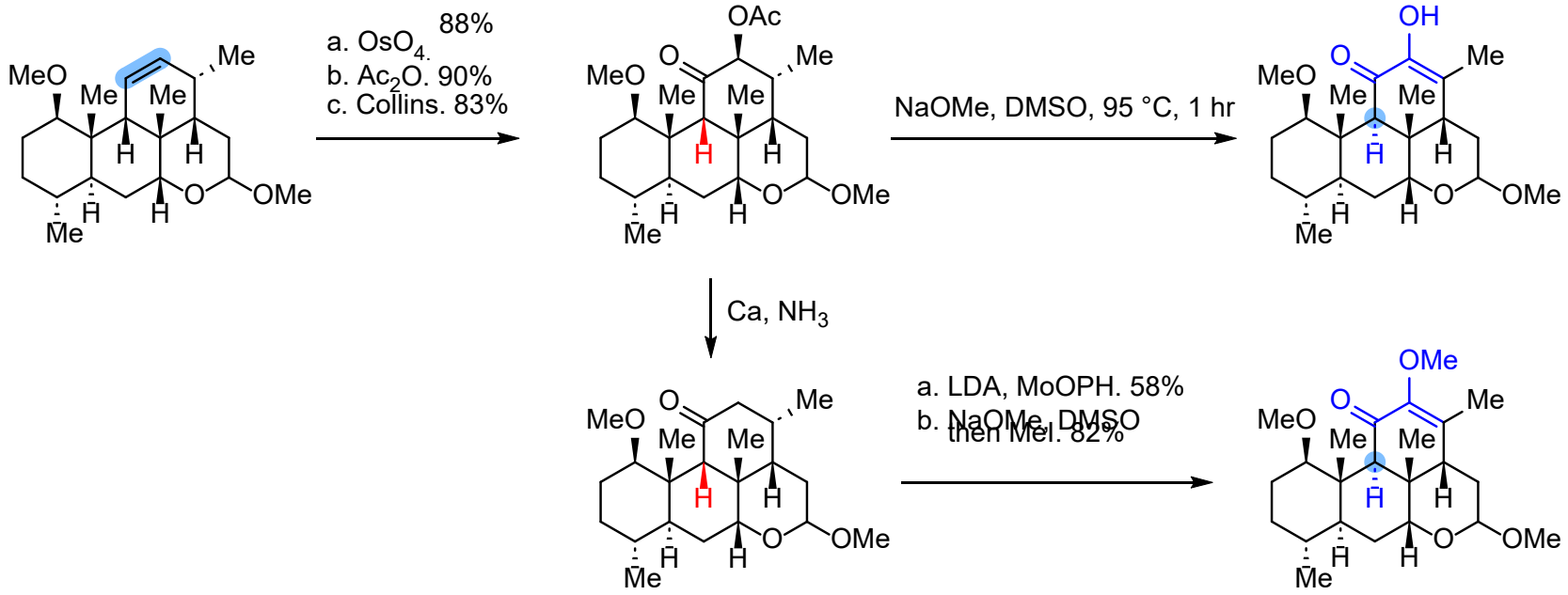
# Through Oxidation of Olefin/Transformations of Epoxides





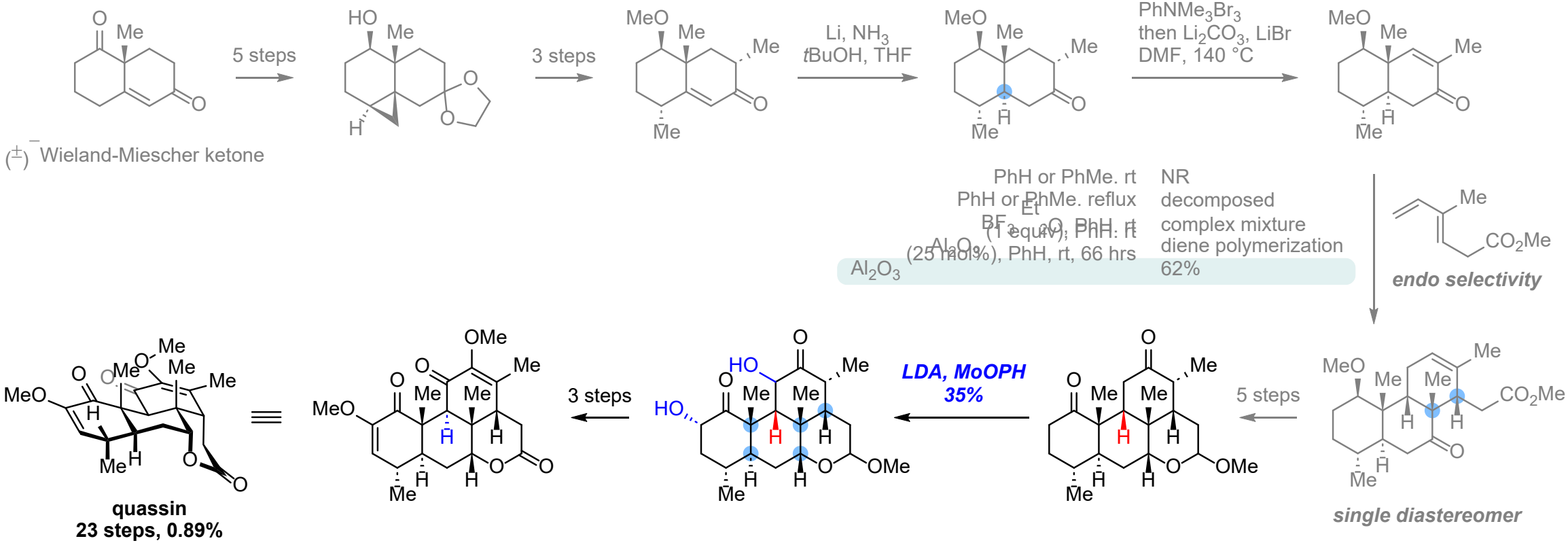
Payne, G. B.; Williams, P. H. *J. Org. Chem.,* **1961**, *26*, 651
Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.,* **1961**, *26*, 659.
Vidari, G.; Ferrino, S.; Grieco, P. A. *J. Am. Chem. Soc.,* **1984**, *106*, 3539

# Olefin Dihydroxylation/Diosphenol Formation



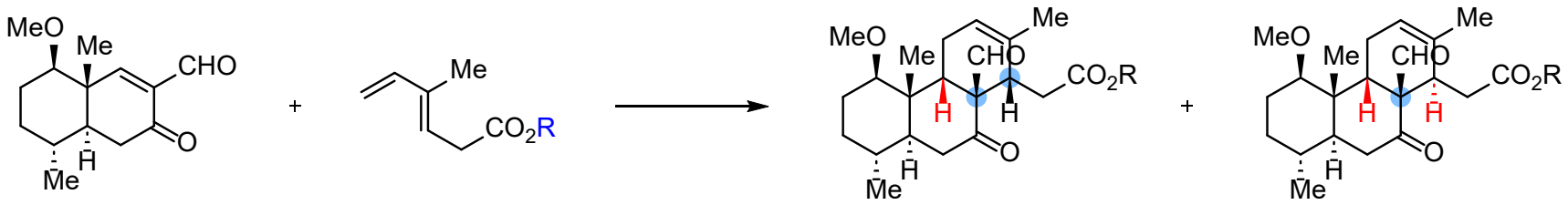

Vidari, G.; Ferrino, S.; Grieco, P. A. *J. Am. Chem. Soc.*, **1984**, *106*, 3539

# The First Racemic Total Synthesis of Quassin (Grieco,1984)




Vidari, G.; Ferrino, S.; Grieco, P. A. *J. Am. Chem. Soc.*, **1984**, *106*, 3539

# “Micellar” Catalysis in Aqueous Intermolecular Diels-Alder Reactions



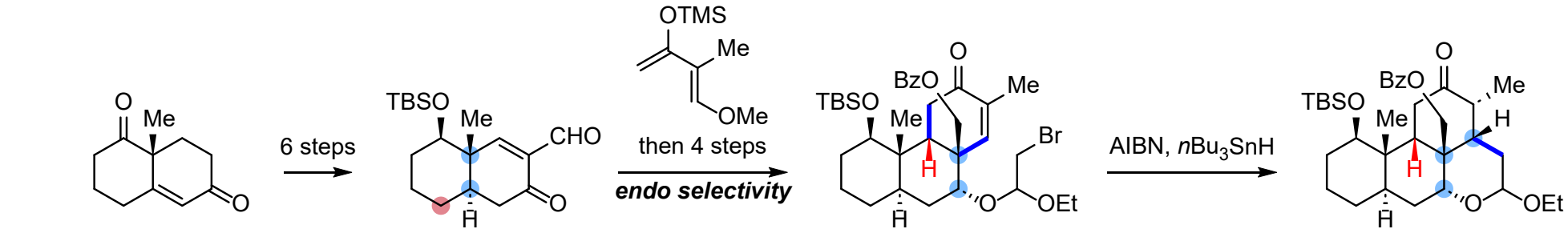

*endo* *exo*

| entry[a] | R | solvent | concentration of diene | time[b] | yield[c] | 14βH/14αH[d] |
|---|---|---|---|---|---|---|
| 1 | Et | benzene | 1.0 M | 288 h | 52%[e] | 0.85 |
| 2 | Et | neat | ----- | 144 h | 69% | 1.3 |
| 3 | Et | water | 1.0 M | 168 h | 82% | 1.3 |
| 4 | H | toluene | 1.0 M | 168 h | 46%[e] | 0.7 |
| 5 | H | neat | ----- | 30 h | 80% | 1.4 |
| 6 | H | water | 1.0 M | 17 h | 85% | 1.5 |
| 7 | H | water-dioxane (1:1) | 1.0 M | 104 h | 100% | 0.8 |
| 8 | H | water-MeOH (1:1) | 1.0 M | 97 h | 99% | 2.0 |
| 9 | Na | water | 0.1 M | 120 h | 46%[e] | 0.9 |
| 10 | Na | water | 1.0 M | 8 h | 83% | 2.0 |
| 11 | Na | water | 2.0 M | 5 h | 100% | 3.0 |

[a]All reactions were run at room temperature employing a five-fold excess of diene over dineophile. [b]Reactions were judged to be complete by TLC analysis. [c]Yields reported are for chromatographically pure mixtures of $C_{14}$ epimers. [d]Ratios were determined by NMR. [e]Starting dienophile was recovered: entry 1 (29%), entry 4 (40%), and entry 9 (14%).

Paul A. Grieco*, Philip Garner and Zhen-min He. *Tetrahedron Lett.,* **1983**, *24*, 18, 1897-1900.

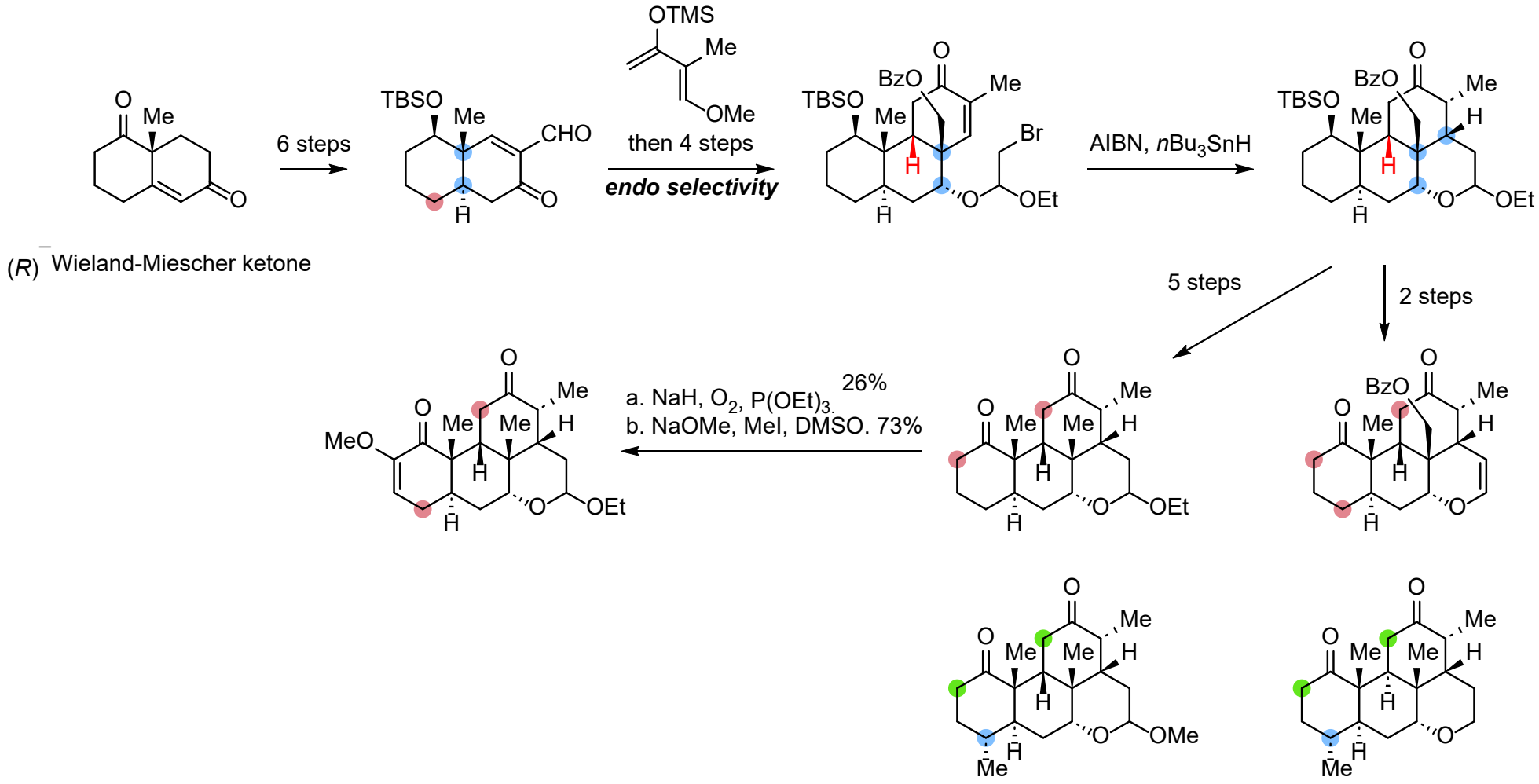
# Initial Modification of Grieco's by Watt (1990)




(*R*) Wieland-Miescher ketone

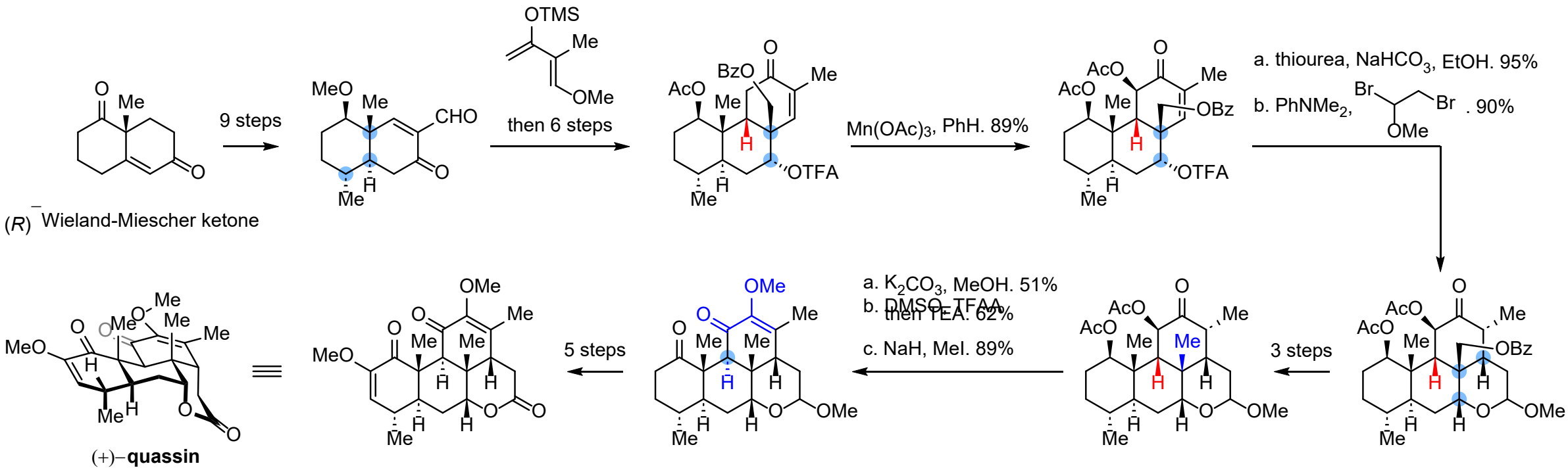
M. Kim, K. Kawada, R. S. Gross and D. S. Watt, *J. Org. Chem.,* **1990**, *55*, 504.

# Initial Modification of Grieco's by Watt (1990)



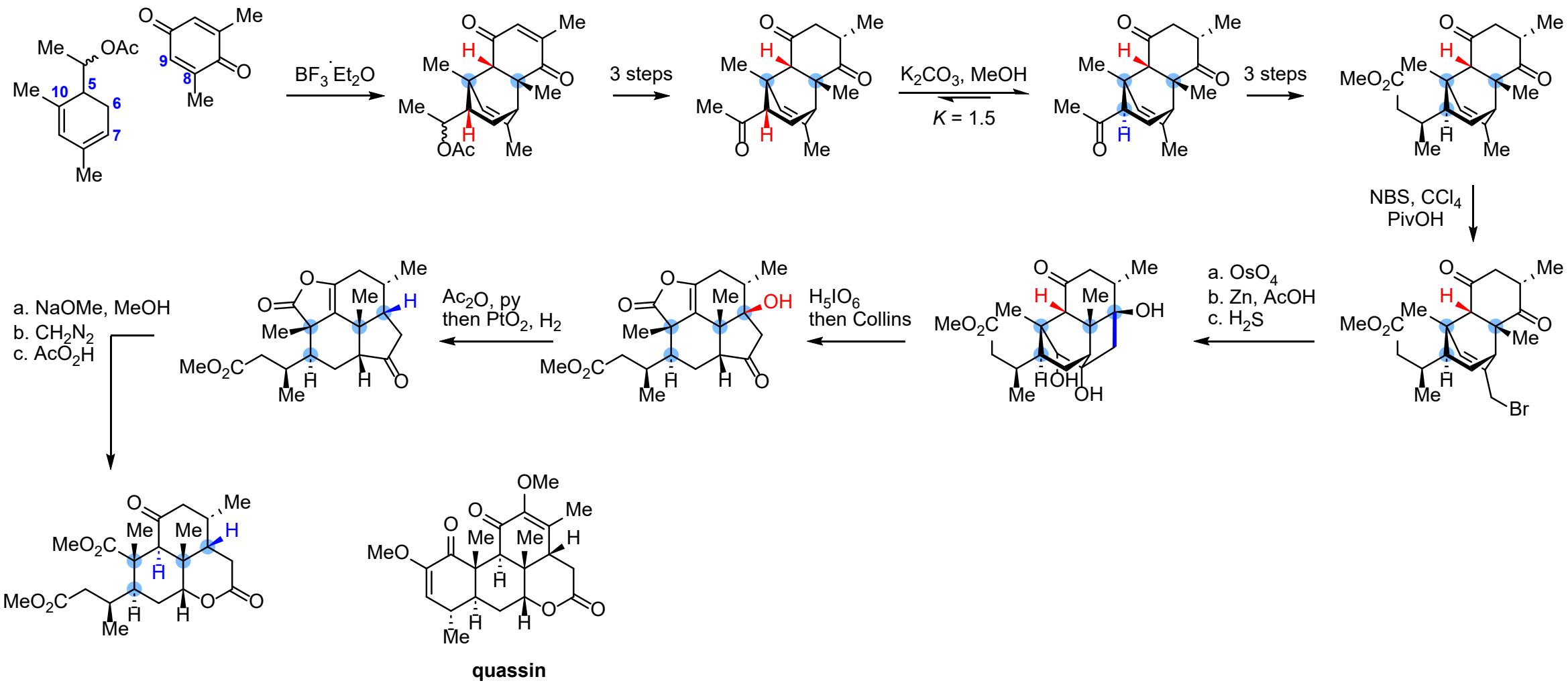

M. Kim, K. Kawada, R. S. Gross and D. S. Watt, *J. Org. Chem.,* **1990**, *55*, 504.

# Final Route to Quassin by Watt (1990)



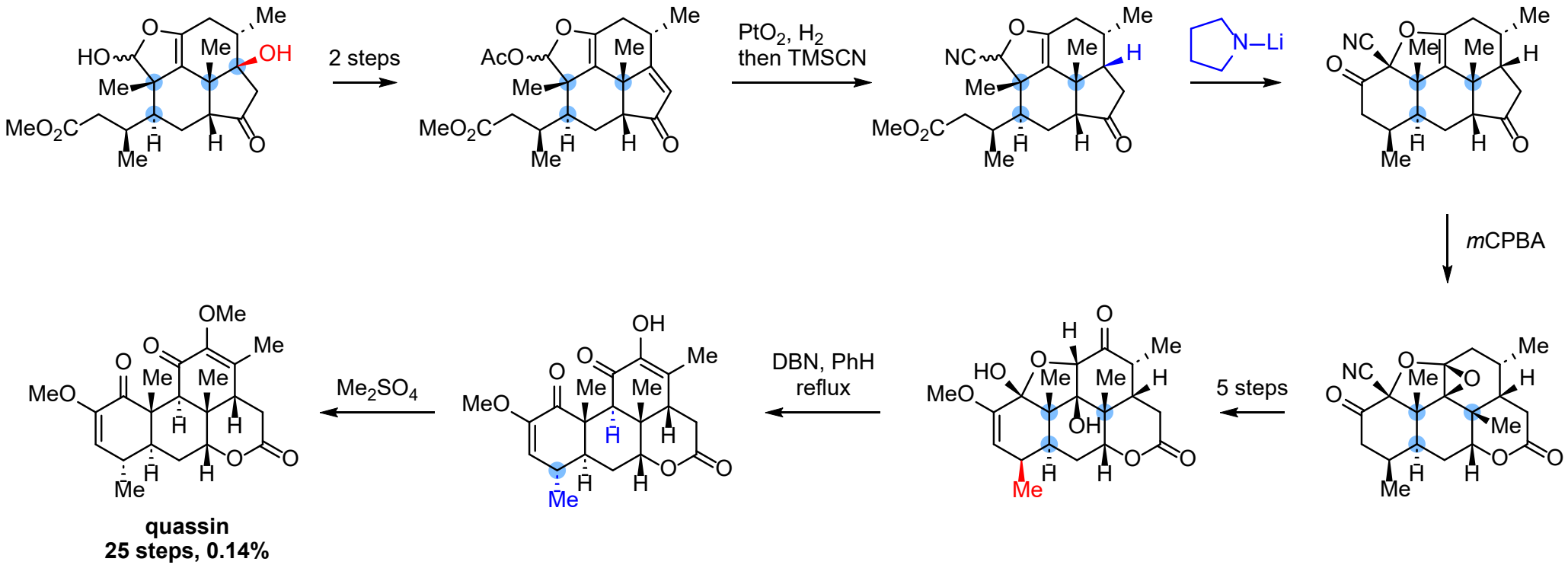

M. Kim, K. Kawada, R. S. Gross and D. S. Watt, *J. Org. Chem.,* **1990**, *55*, 504.

# Pioneering Design (Valenta, 1975, 1979)



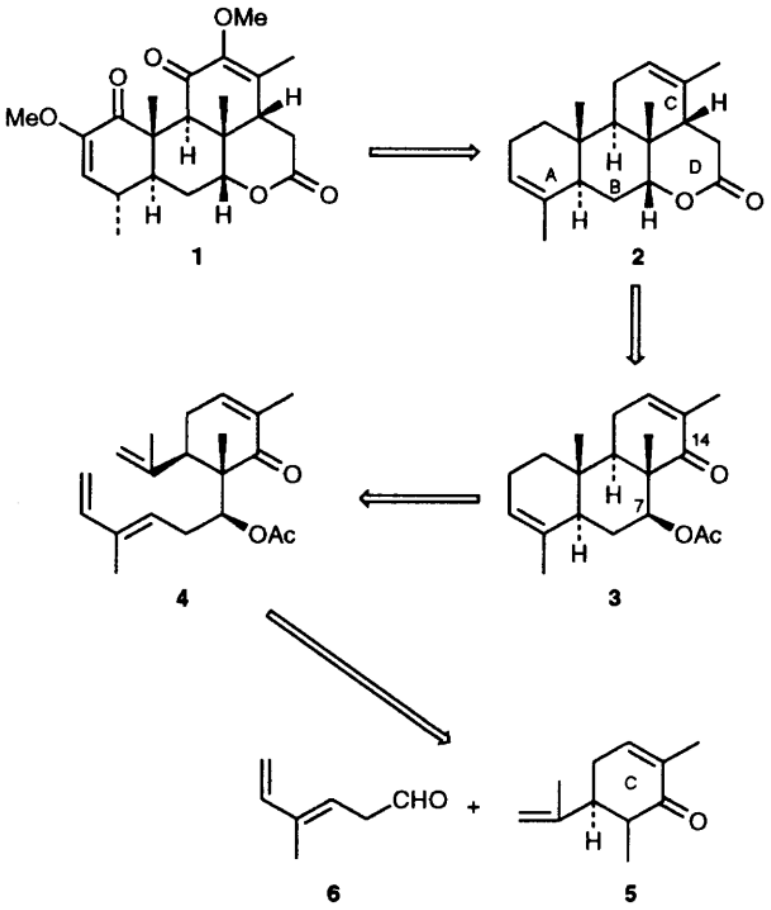

N. Stojanac, A. Sood, Z. Sojanac and Z. Valenta*, *Can. J. Chem.*, **1975**, *53*, 619.
N. Stojanac, Z. Sojanac, P. S. White and Z. Valenta*, *Can. J. Chem.*, **1979**, *57*, 3346.

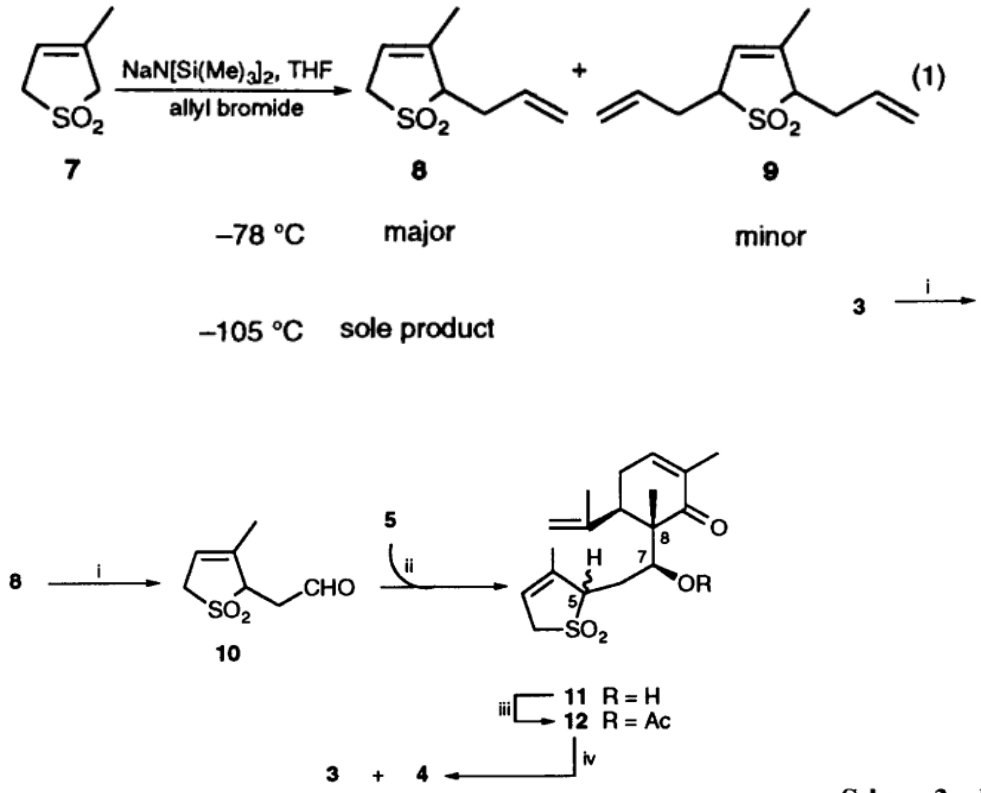
# Racemic Total Synthesis of Quassin (Valenta,1991)



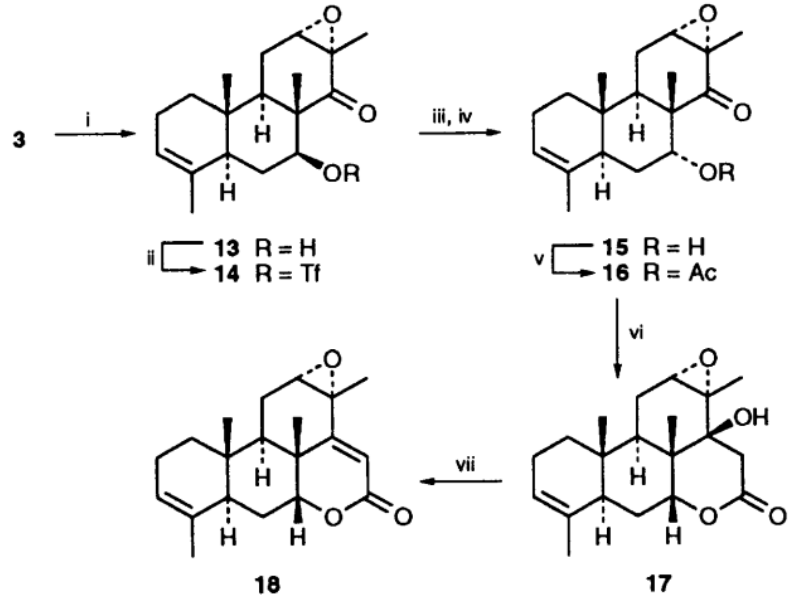

Stojanac, H.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 853.

# Construction of A/B Ring by Intramolecular DA to Quassin Synthesis (Shing, 1994)



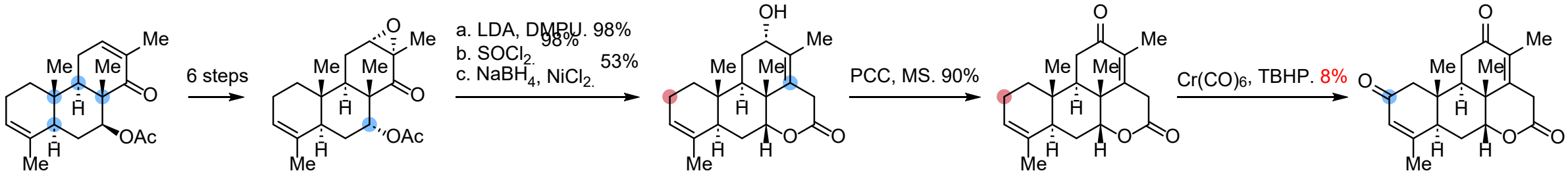

**Scheme 2** *Reagents and conditions:* i, $OsO_4$, MNO, aq. 1,4-dioxane; then $NaIO_4$, aq. MeOH (60%); ii, LDA, followed by aldehyde **10**, THF, DMPU, −78 °C (87%); iii, $Ac_2O$, pyridine, DMAP, $CH_2Cl_2$, room temp. (89%); iv, PhCN, Methylene Blue, 190 °C, 110 h (62%)




**Scheme 3** *Reagents and conditions:* i, $Bu^tO_2H$, Triton B, MeOH; then KOH, MeOH (85%); ii, $Tf_2O$, pyridine, DMAP, $CH_2Cl_2$,0 °C; iii, wet DMF, room temp.; iv, $K_2CO_3$, MeOH, room temp. (60%); v, $Ac_2O$, pyridine, DMAP, $CH_2Cl_2$, room temp. (100%); vi, LDA, THF, DMPU, −78 to 0 °C (98%); vii, $SOCl_2$, pyridine, 0 °C (98%)

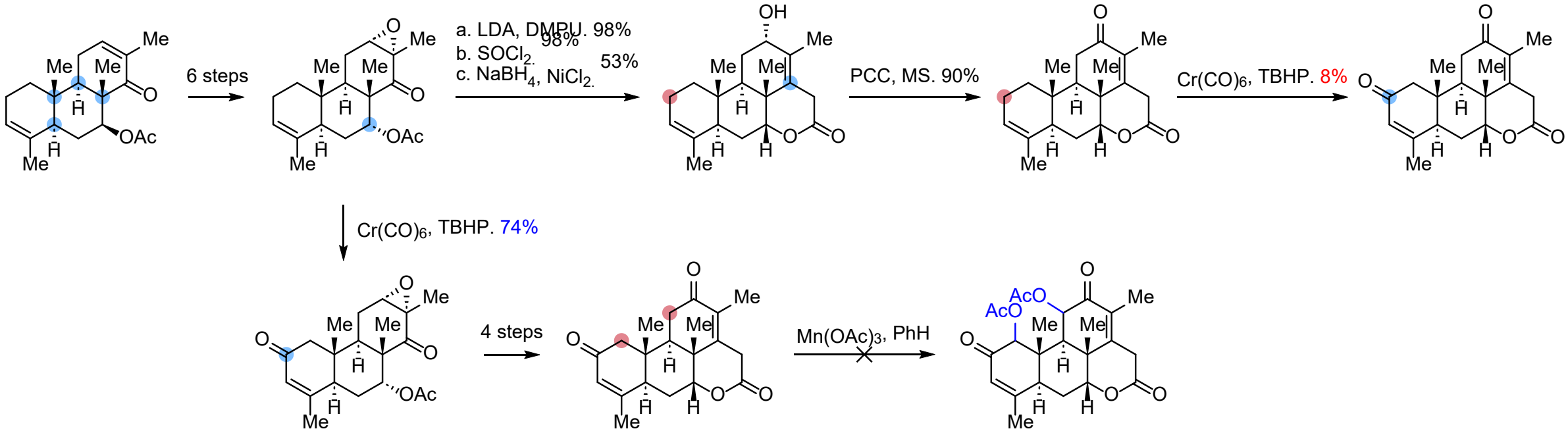

Shing, T. K. M.; Tang, Y. *J. Chem. Soc., Perkin Trans. 1.* **1994**, 1625.
T. K. M. Shing and Q. Jiang, *J. Org. Chem.*, **2000**, *65*, 7059.

# Fruitless Oxidation Protocols of Substrates with Lactone (Shing, 2000)



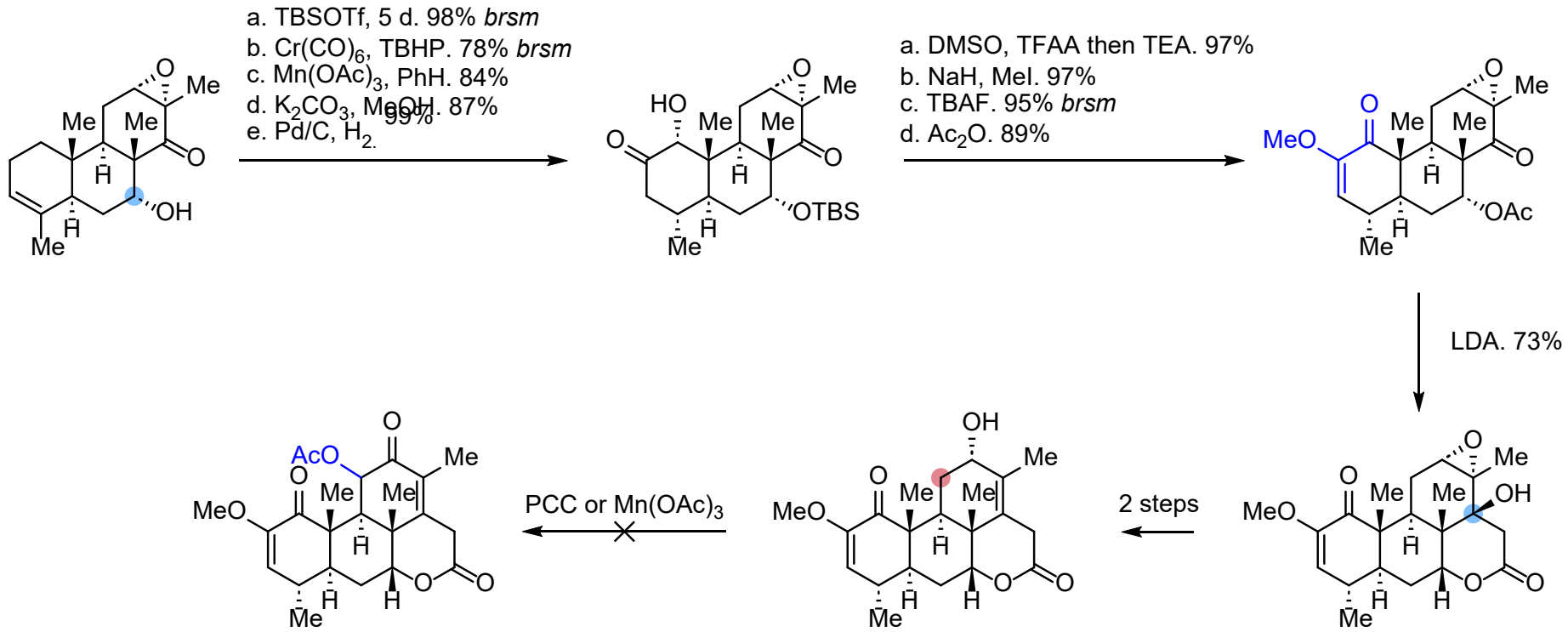

T. K. M. Shing and Q. Jiang, *J. Org. Chem.*, **2000**, *65*, 7059.

# Fruitless Oxidation Protocols of Substrates with Lactone (Shing, 2000)



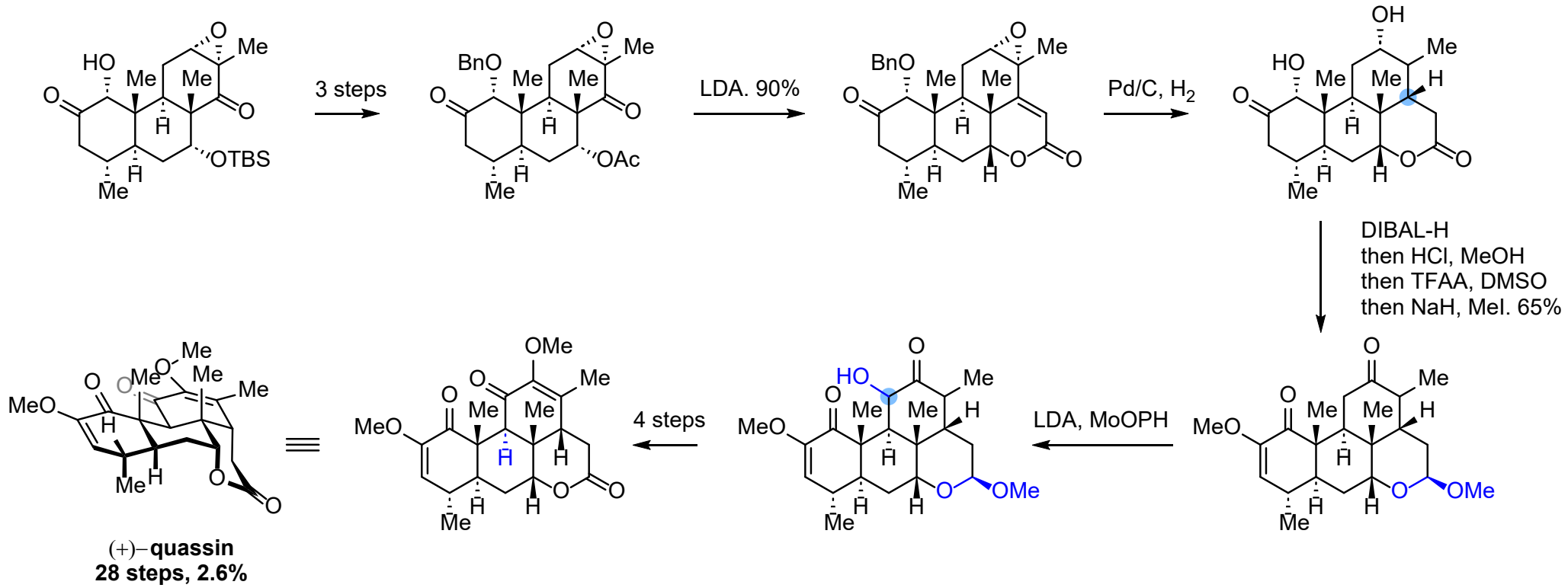

T. K. M. Shing and Q. Jiang, *J. Org. Chem.*, **2000**, *65*, 7059.

# Fruitless Oxidation Protocols of Substrates with Lactone (Shing, 2000)



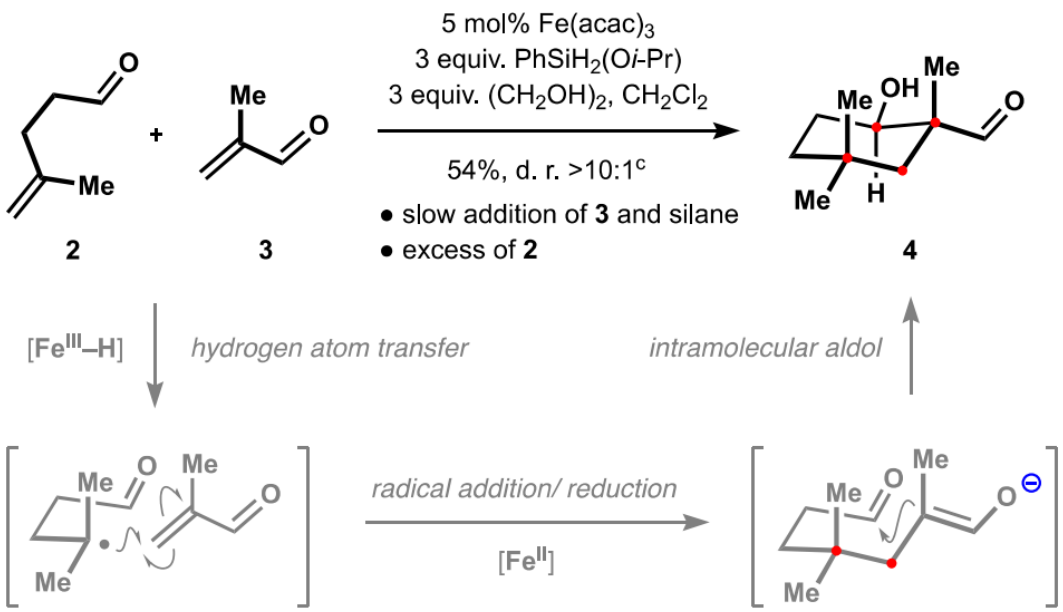

T. K. M. Shing and Q. Jiang, *J. Org. Chem.*, **2000**, *65*, 7059.

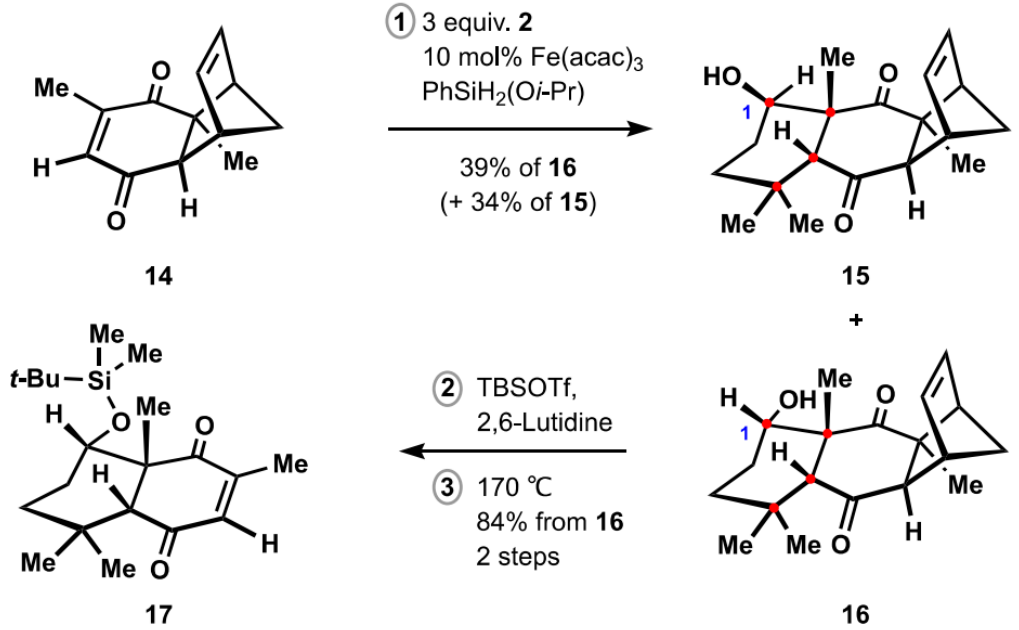
# Enolate Oxygenation Furnished The Synthesis(Shing, 2000)




T. K. M. Shing and Q. Jiang, *J. Org. Chem.*, **2000**, *65*, 7059.

# Radical Intermolecular Reductive Coupling

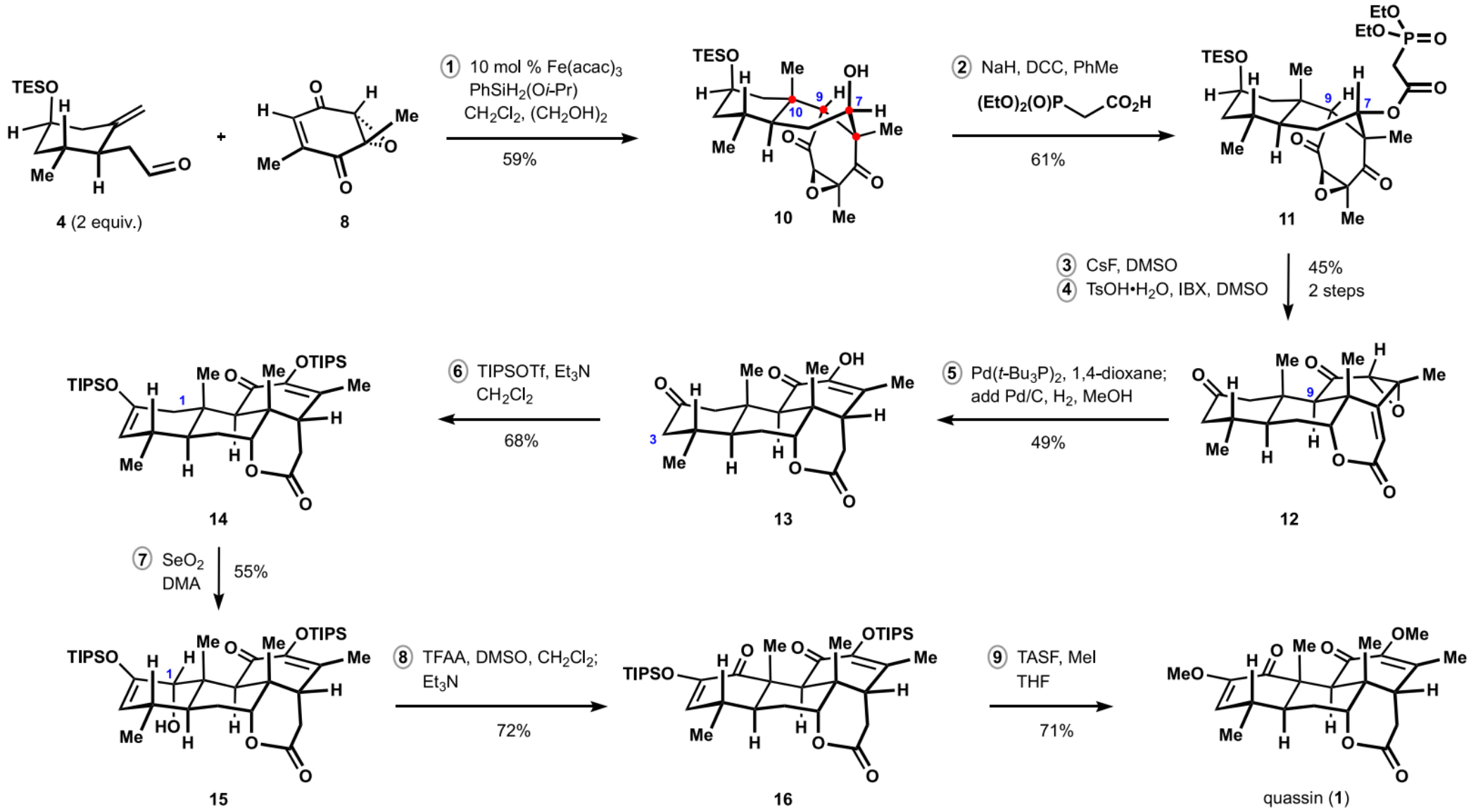




Julian C. Lo, Yuki Yabe, and Phil S. Baran. *J. Am. Chem. Soc.*, **2014**, *136*, 1304−1307.
William P. Thomas, Devon J. Schatz, David T. George, and Sergey V. Pronin*. *J. Am. Chem. Soc.*, **2019**, *141*, 12246−12250.

# Radical Approach to the Concise Synthesis of Quassin (Pronin, 2022)

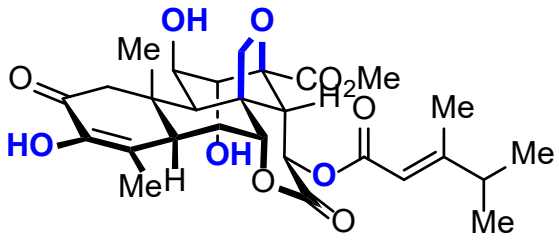



William P. Thomas and Sergey V. Pronin*. *J. Am. Chem. Soc.*, **2022**, *144*, 118−122.

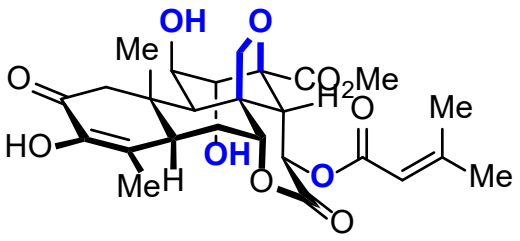
# Outline

- Introduction – Phytochemistry and Basic structures
- Synthetic studies toward quassin
  - Preliminary investigations
  - Total synthesis of quassin
- **Total synthesis of other quassinoids**
- Synthetic studies of core structure of quassinoids
- Summary

# Bruceantin

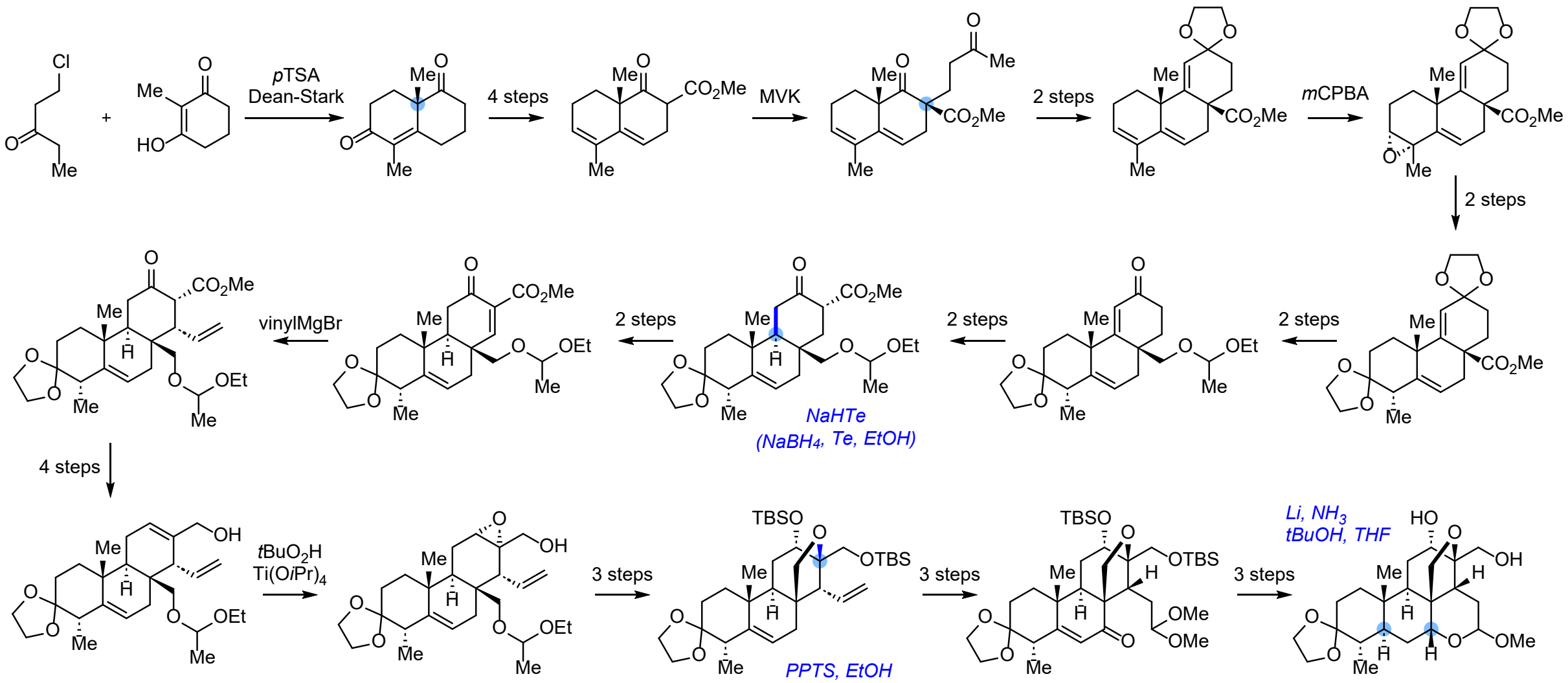



**bruceantin**




**brusatol**

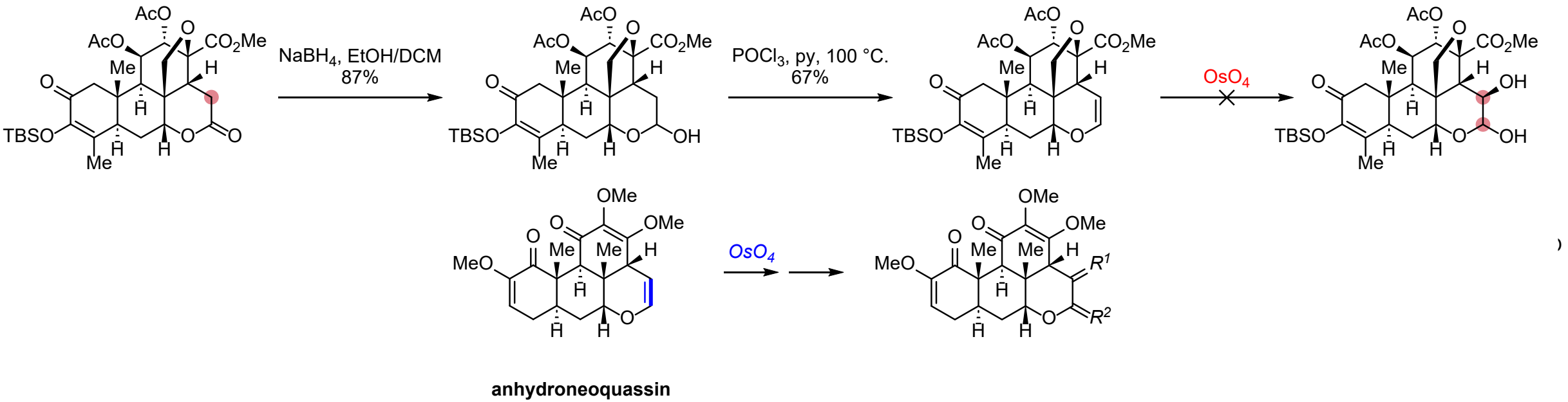
# Synthesis of Bruceantin Skeleton (Murae, 1986)





Yamashita, M.; Kato, Y.: Suemitsu, *M. Chem. Lett.*, **1980**, 847.
Murae, T.; Sasaki, M.; Konosu, T.; Matsuo, H.; Takahashi, T., *Tetrahedron Lett.*, **1986**, *27*, 3411.

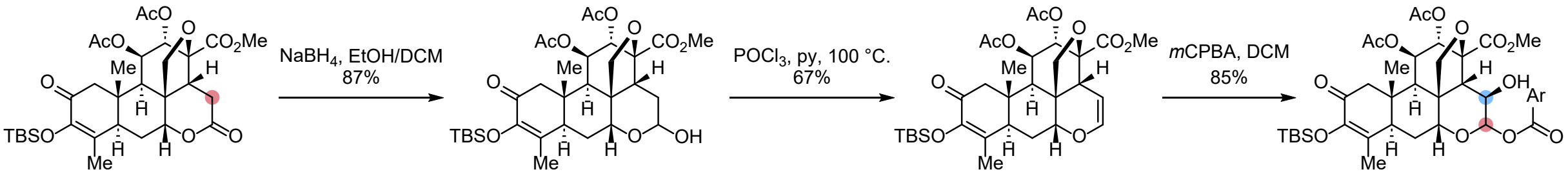
# Failed Dihydroxylation (Murae, 1989)




**anhydroneoquassin**

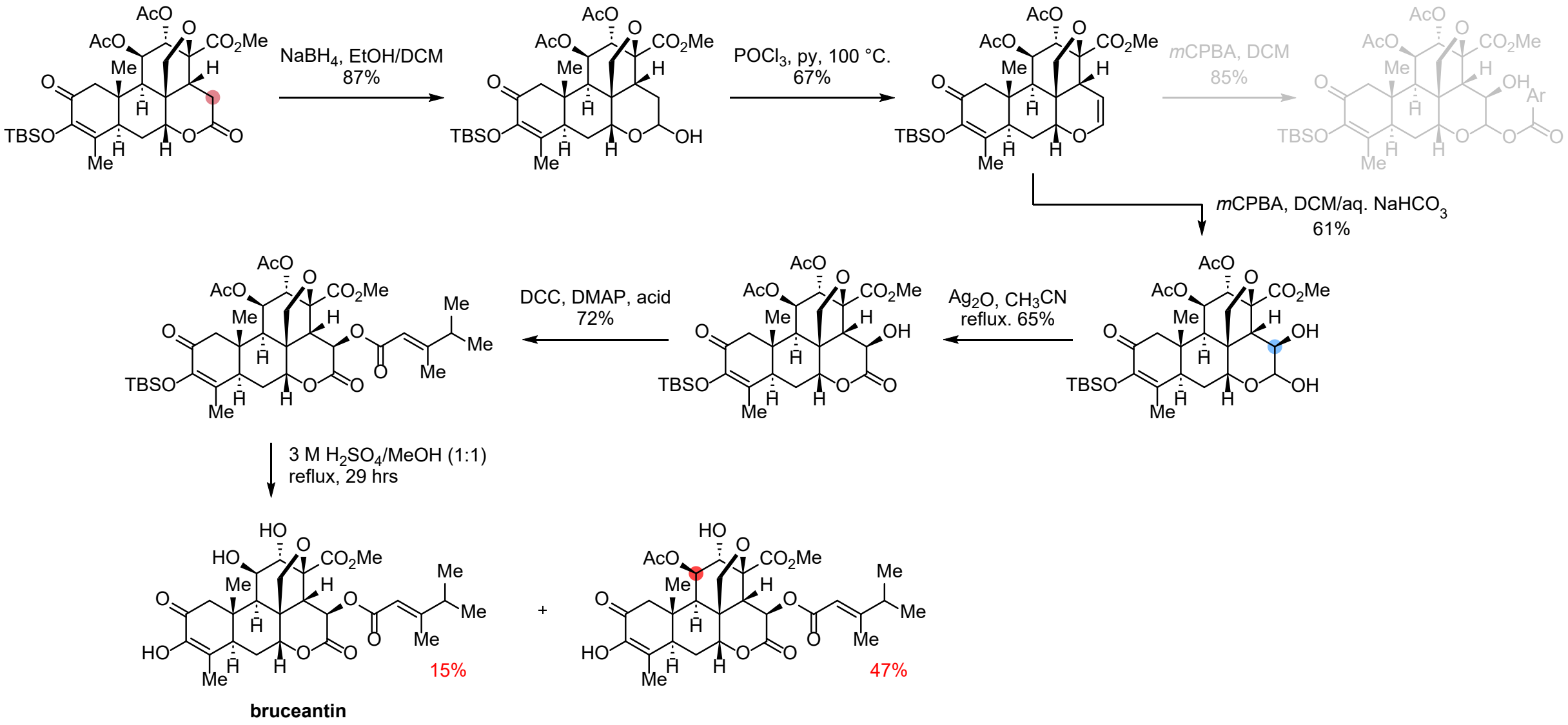

Murae, T.: Takahashi, T., *Bull. Chem. Soc. Jpn.*, **1981**, *54*, 941.
Sasaki, M.; Murae, T. *Tetrahedron Lett.*, **1989**, *30*, 355.

# Finished the Synthesis (Murae, 1989)




Sasaki, M.; Murae, T. *Tetrahedron Lett.,* **1989**, *30*, 355.

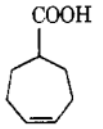
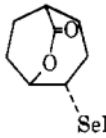
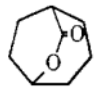
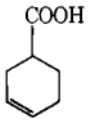
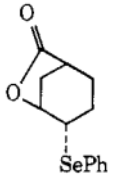
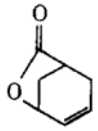
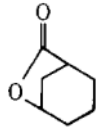
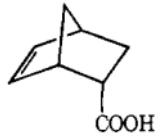
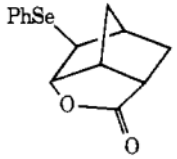
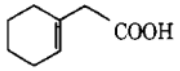
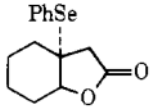
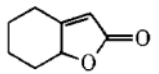
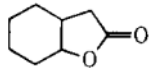
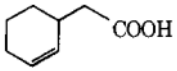
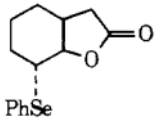
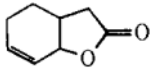
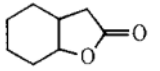
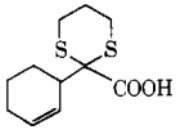
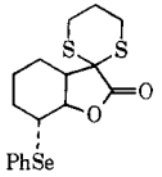
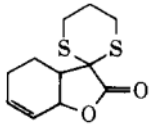
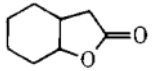
# Finished the Synthesis (Murae, 1989)




Sasaki, M.; Murae, T. *Tetrahedron Lett.* **1989**, *30*, 355.

# Existing Approaches for Construction of C8-C13 Epoxy Methano Bridge

**Table I.** Phenylselenolactonization and Useful Transformations of Phenylselenolactones

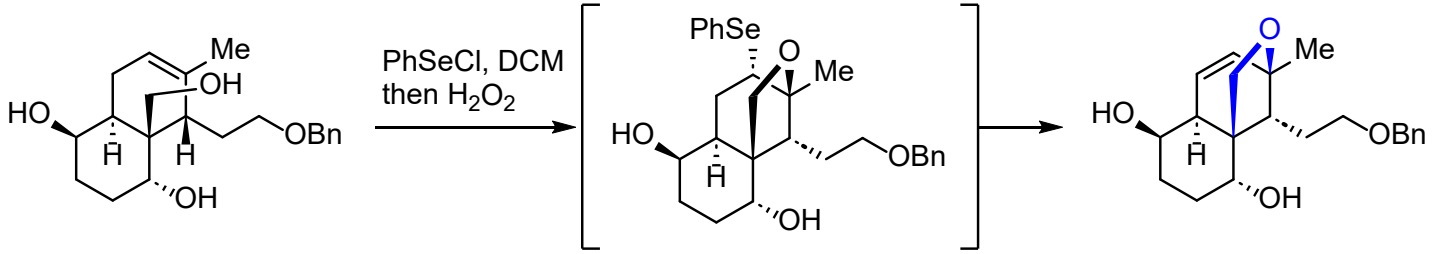
| Entry | Unsaturated acid | Ref | Phenylseleno-lactone | Yield (%) | Unsaturated lactone | Yield (%) | Saturated lactone | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 |  | 11a |  | 100 |  | 90 |  | 85 |
| 2 |  | 11b |  | 90 |  | 81 |  | 80 |
| 3 |  | 11c |  | 95 | a | |  | 83 |
| 4 |  | 11d |  | 91 |  | 87 |  | 84 |
| 5 |  | 11e |  | 93 |  | 92 |  | 76 |
| 6 |  | 11f |  | 98 |  | 82 |  | 73 |

[a] The elimination of the corresponding selenoxide has not been studied in detail yet.

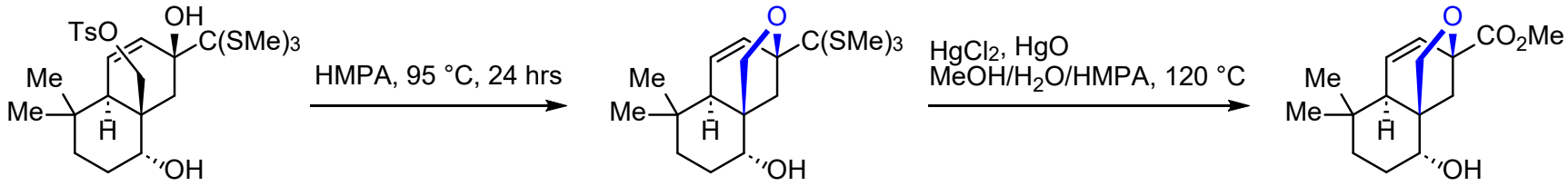
Nicolaou, K. C.; Lysenko, Z. *J. Am. Chem. Soc.*, **1977**, *99*, 3185.

# Existing Approaches for Construction of C8-C13 Epoxy Methano Bridge

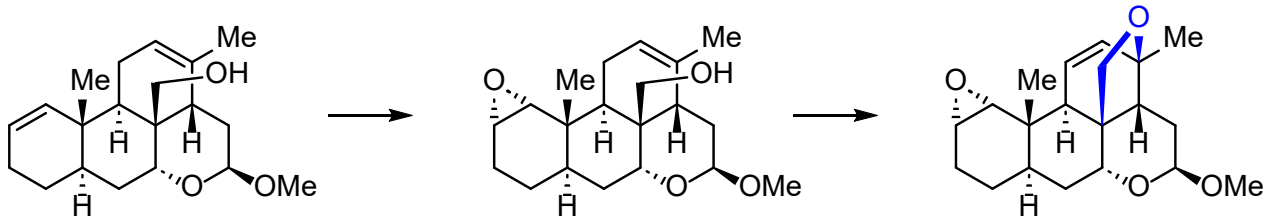
**Kraus, 1980**




**Fuchs, 1980**



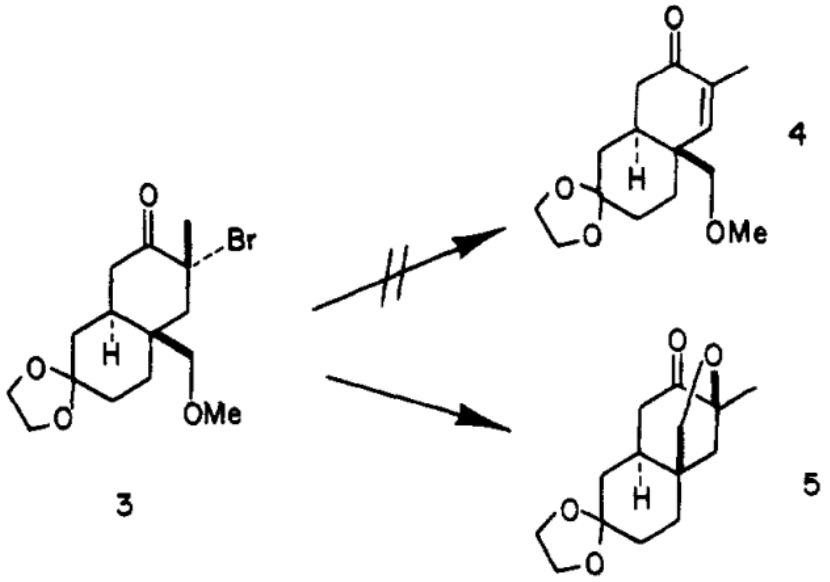

**Ganem, 1984**





Dailey, O. D., Jr.; Fuchs, P. L. *J. Org. Chem.,* **1980**, *45*, 216.
Kraus, G. A.; Taschner, M. J. *J. Org. Chem.,* **1980**, *45*, 1175.
Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.,* **1984**, *106*, 3353.

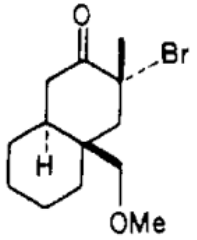
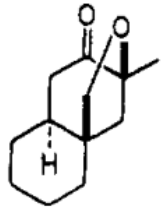
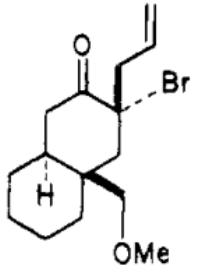
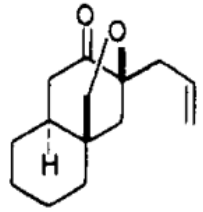
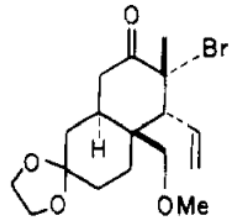
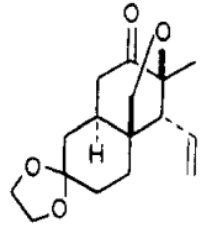
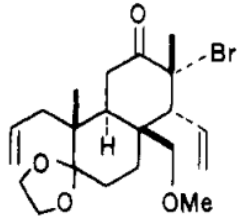
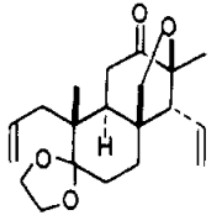
# Unexpected Transformation (Grieco, 1984)




Ken-ichi Kanai, Robert E. Zelle, Hing-Lueng Sham Paul A. Grieco*, Paul Gallant. *J. Org. Chem.,* **1984**, *49*, 3867-3868.

# Unexpected Transformation (Grieco, 1984)

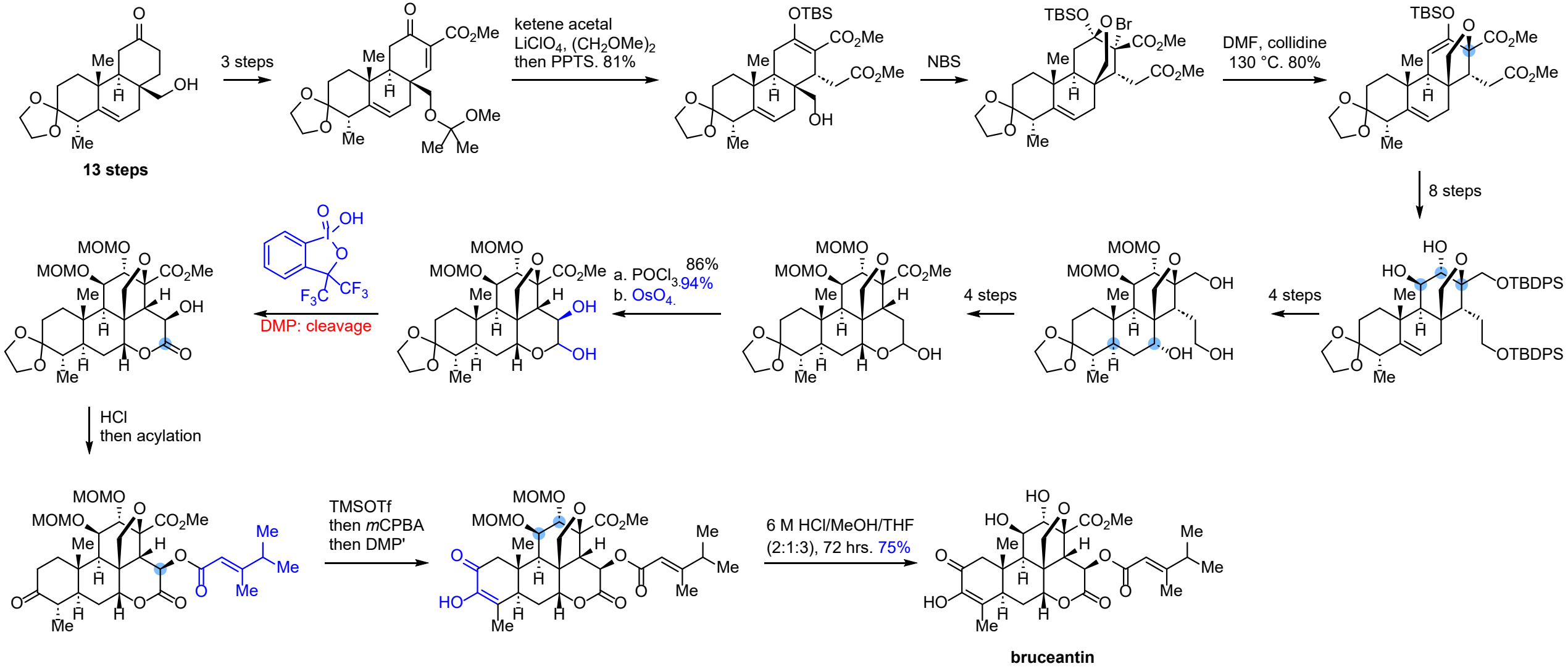
**Table I. Epoxymethano Bridge Formation**[a]

| substrate | product | yield |
|---|---|---|
|  8[8] |  9 | 93% |
|  10[8] |  11 | 88% |
|  12[9] |  13 | 91% |
|  14[11] |  15 | 90% |

[a] All reactions were carried out at 140 °C for 20 min in DMF.

Ken-ichi Kanai, Robert E. Zelle, Hing-Lueng Sham Paul A. Grieco*, Paul Gallant. *J. Org. Chem.,* **1984**, *49*, 3867-3868.

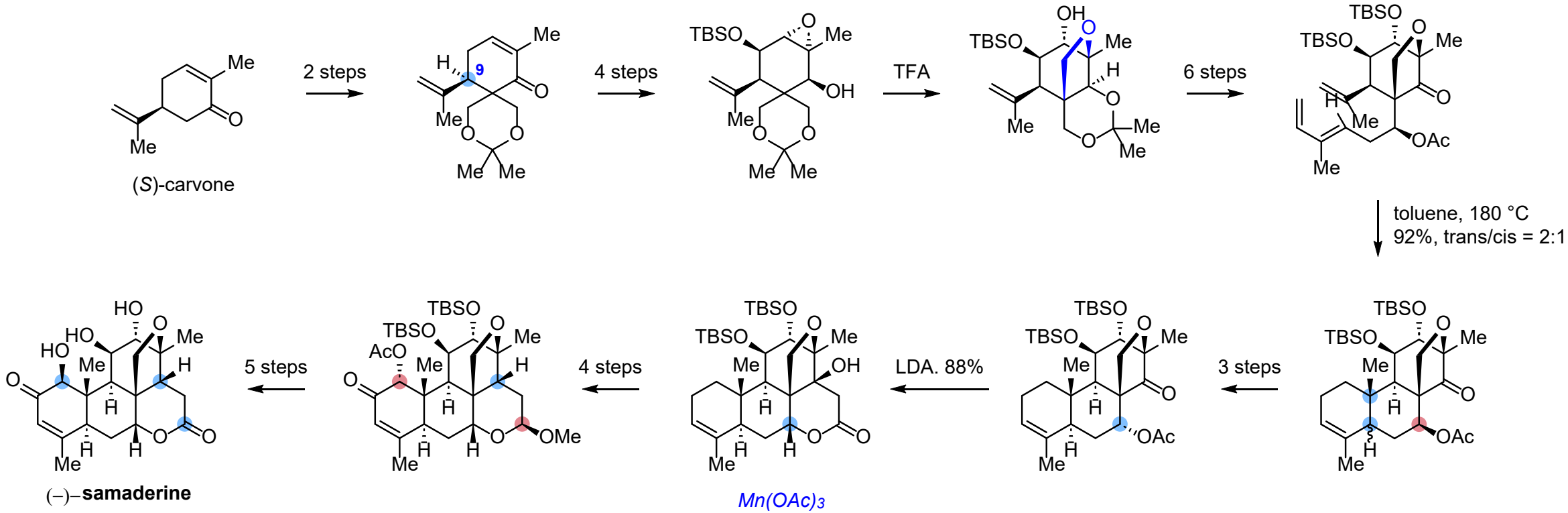
# A More Effective Route to Bruceantin (Grieco, 1993)





Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.*, **1991**, *113*, 7277.
J. M. Vander Roest and P. A. Grieco, *J. Am. Chem. Soc.*, **1993**, *115*, 5841.

# 21-Step Synthesis of Samaderine (Shing, 2005)

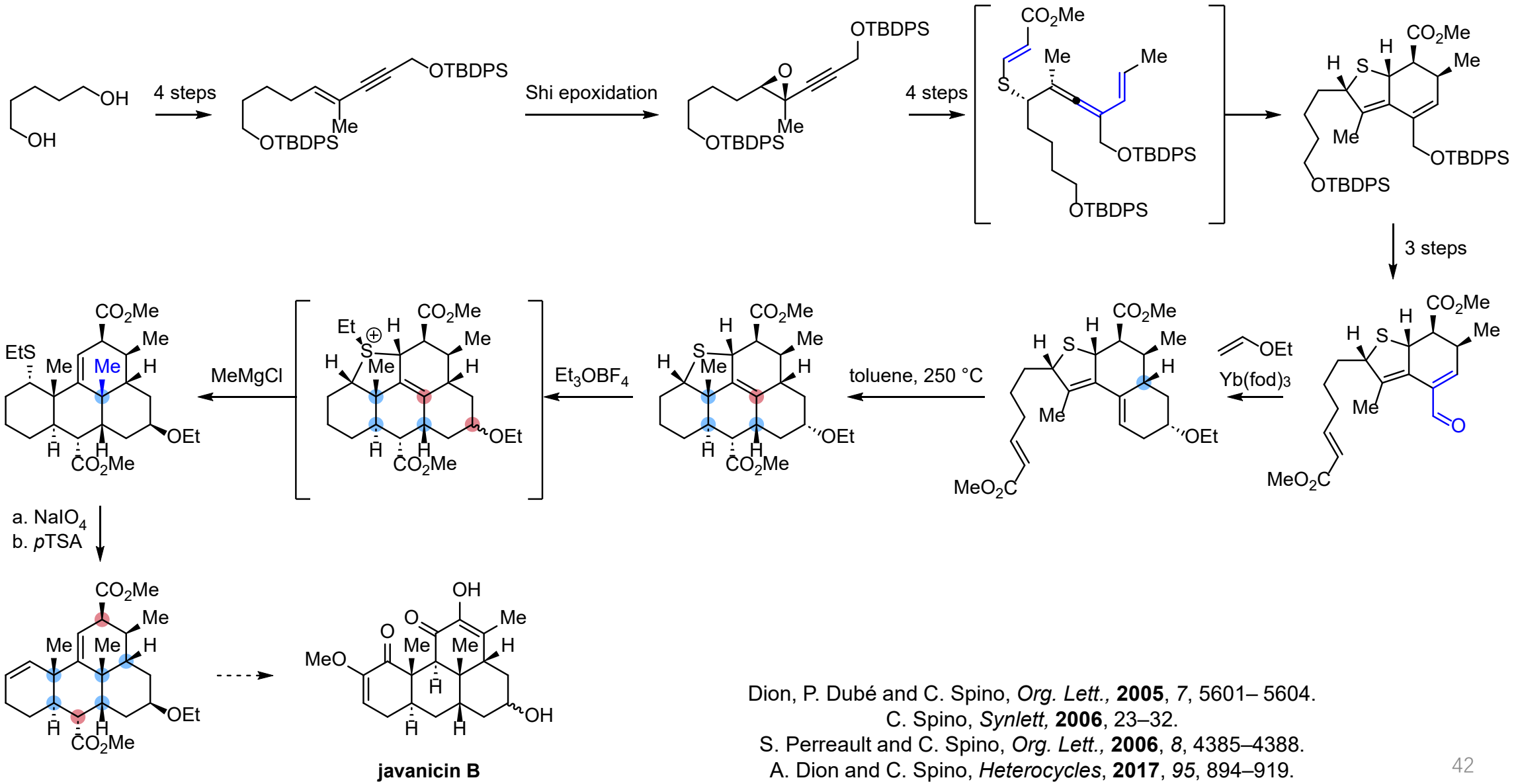



T. K. M. Shing and Y. Y. Yeung, *Angew. Chem., Int. Ed.*, **2005**, *44*, 7981–7984.

# Outline

- Introduction – Phytochemistry and Basic structures
- Synthetic studies toward quassin
  - Preliminary investigations
  - Total synthesis of quassin
- Total synthesis of other quassinoids
- **Synthetic studies of core structure of quassinoids**
- Summary

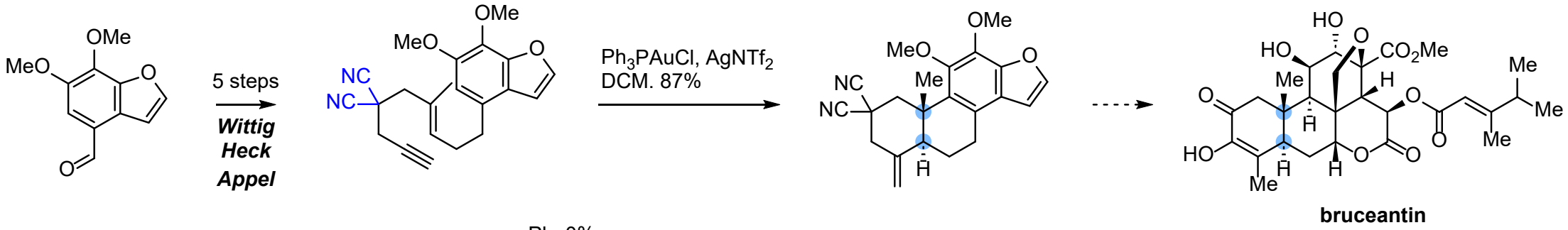
# Synthesis of Framework of Javanicin B Through Consecutive *DA* Reaction (Spino)





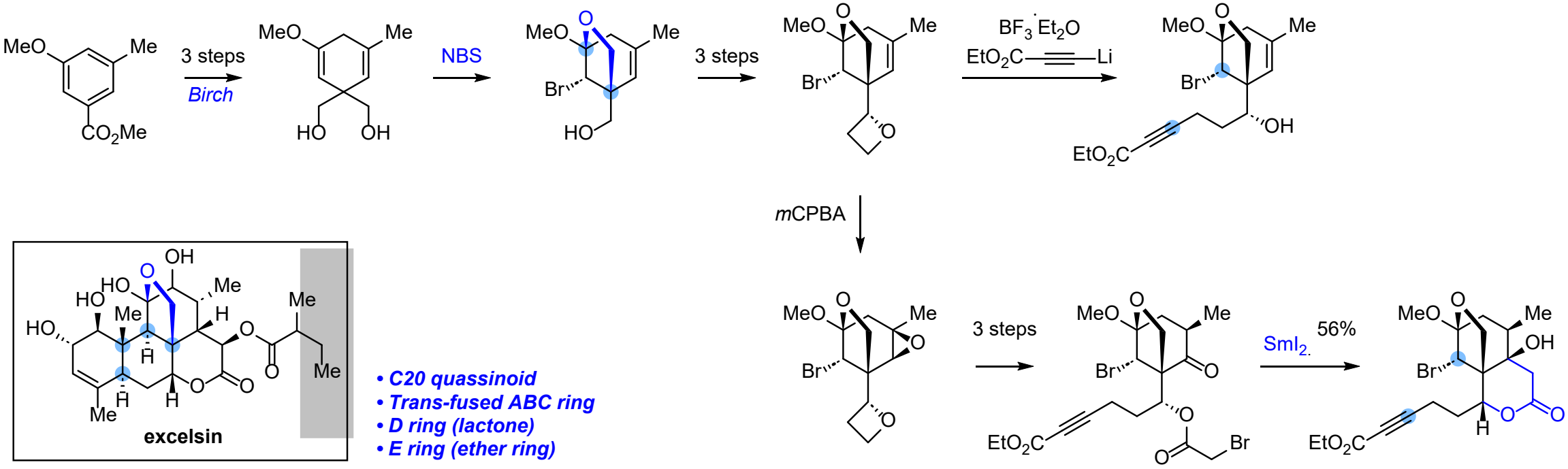
Dion, P. Dubé and C. Spino, *Org. Lett.,* **2005**, *7*, 5601– 5604.
C. Spino, *Synlett,* **2006**, 23–32.
S. Perreault and C. Spino, *Org. Lett.,* **2006**, *8*, 4385–4388.
A. Dion and C. Spino, *Heterocycles*, **2017**, *95*, 894–919.

# Gold-Catalyzed Ene-yne Cyclization



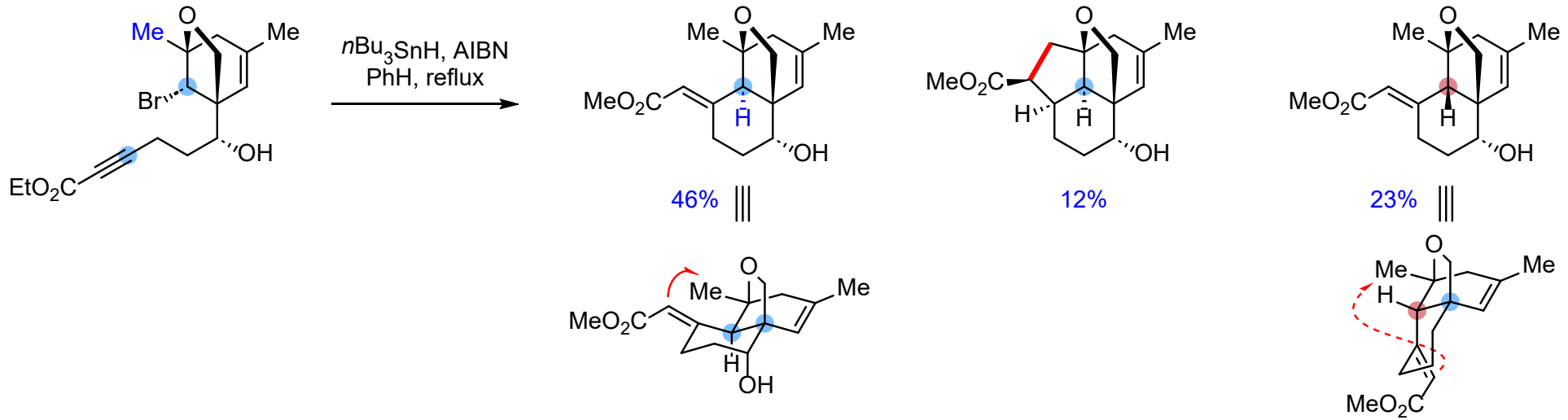

Y. Oki and M. Nakada. *Tetrahedron Lett.,* **2018**, *59*, 926– 929.

# Radical Cyclization Approach to Construct B-ring



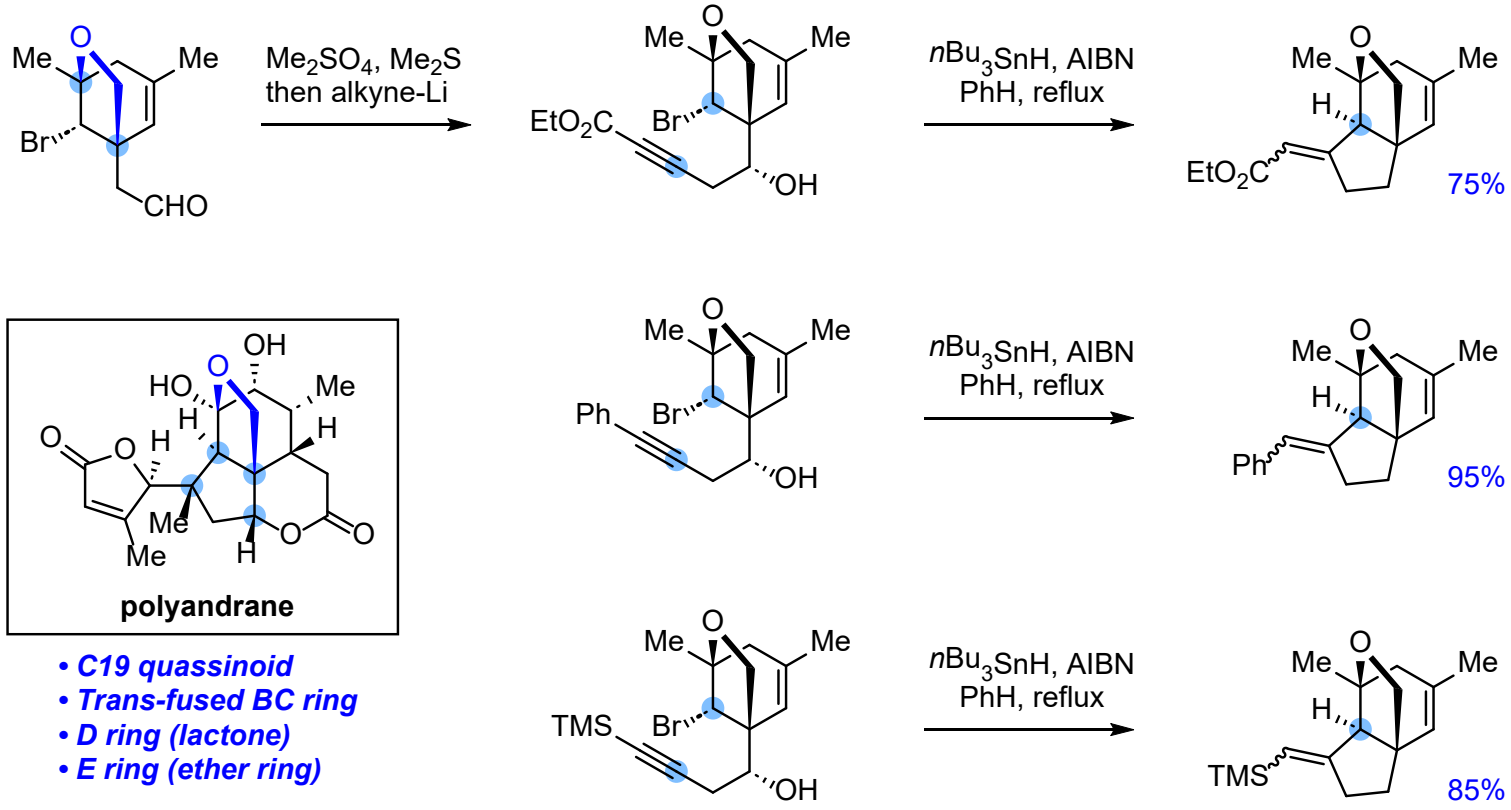

M. G. Donahue and D. J. Hart. *Can. J. Chem.*, **2004**, *82*, 314–317.

# Radical Cyclization Approach to Construct B-ring




M. G. Donahue and D. J. Hart. *Can. J. Chem.*, **2004**, *82*, 314–317.

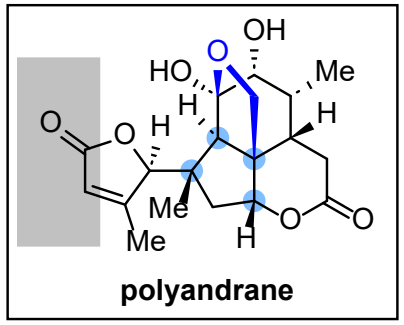
# Radical Cyclization Approach to Construct 5-membered B-ring



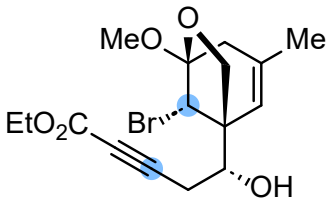

- ***C19 quassinoid***
- ***Trans-fused BC ring***
- ***D ring (lactone)***
- ***E ring (ether ring)***

M. G. Donahue and D. J. Hart. *Can. J. Chem.*, **2004**, *82*, 314–317.

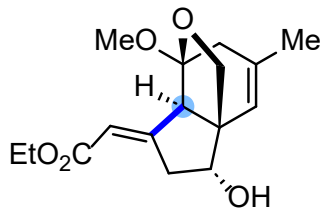
# Radical Cyclization Approach to Construct 5-membered B-ring



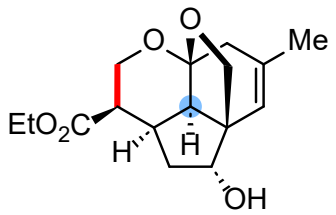

**polyandrane**



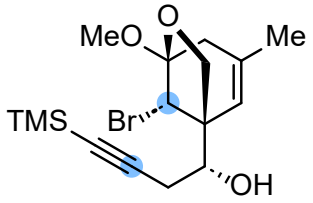

$n$Bu$_3$SnH, AIBN
PhH, reflux



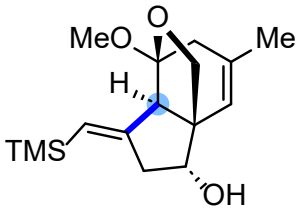

Excess [Sn]-H: 75%



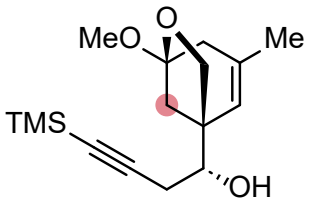

High dilution: 64%



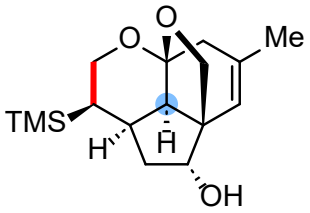

$n$Bu$_3$SnH, AIBN
PhH, reflux



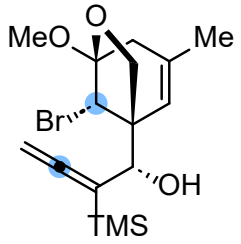

11%



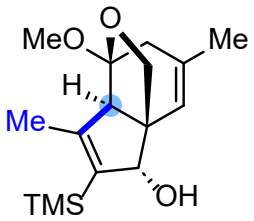

60%




18%
High dilution: 64%



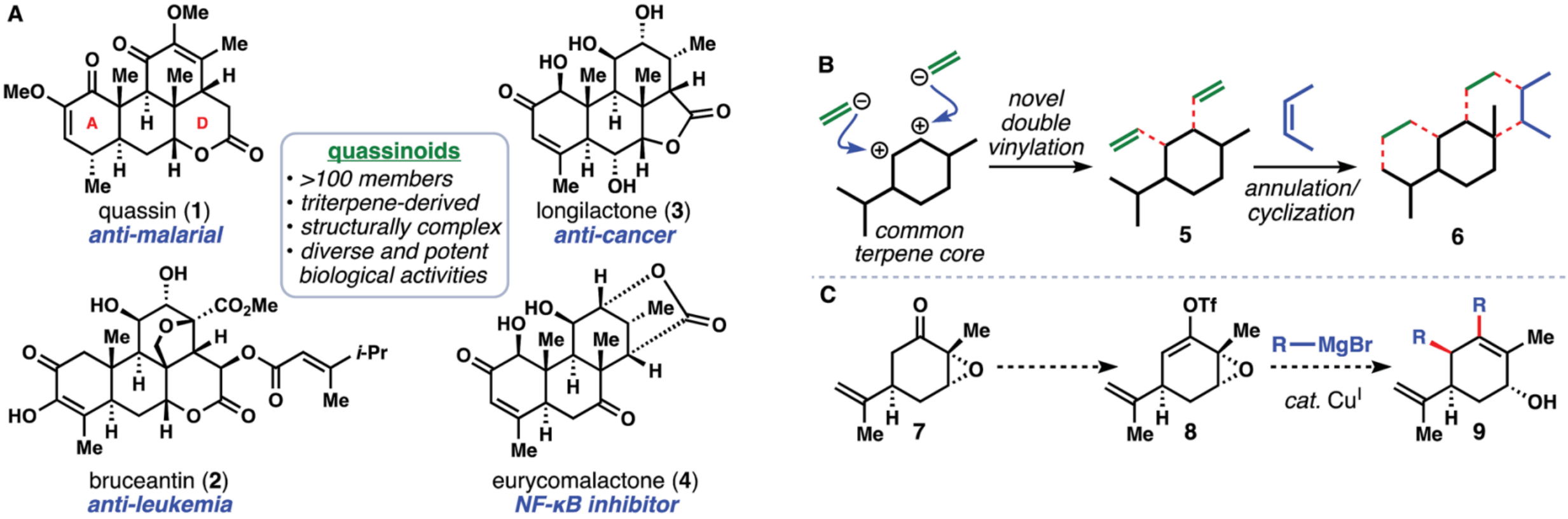

$n$Bu$_3$SnH, AIBN
PhH, reflux




95%

M. G. Donahue and D. J. Hart. *Can. J. Chem.*, **2004**, *82*, 314–317.

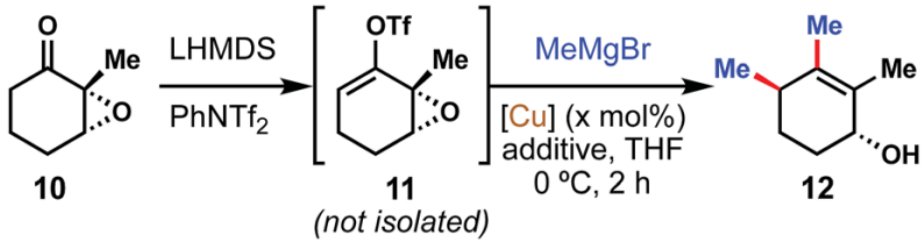
# Quick Assembling of Quassinoid Architecture




M. L. Condakes, R. Z. Rosen, S. J. Harwood and T. J. Maimone. *Chem. Sci.,* **2019**, *10*, 768–772.

# Quick Assembling of Quassinoid Architecture

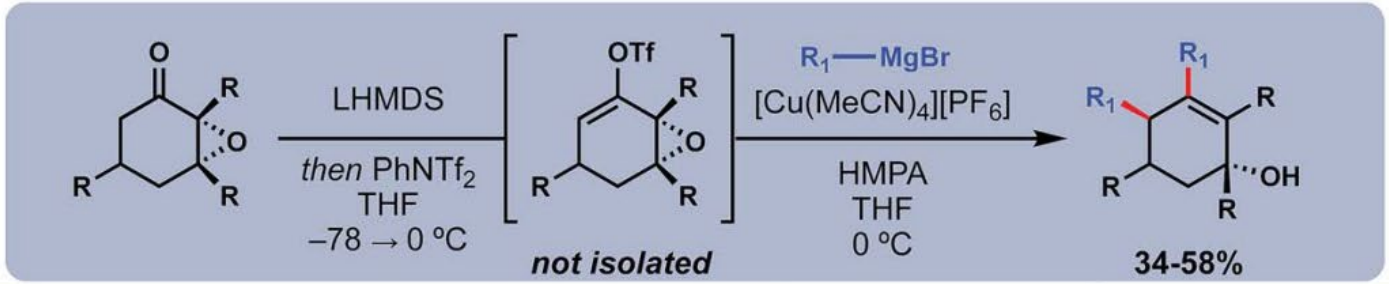
Table 1 Selected optimization studies[a]



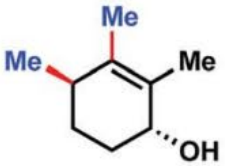

| Entry | [Cu] | $X^b$ (mol%) | Additive[c] | Yield[d] (%) | d.r.[e] |
|---|---|---|---|---|---|
| 1 | CuCl | 15 | — | 43% | 3 : 1 |
| 2 | CuBr | 15 | — | 42% | 3 : 1 |
| 3 | CuI | 15 | — | 43% | 4 : 1 |
| 4 | $[Cu(MeCN)_4][PF_6]$ | 15 | — | 43% | 7 : 1 |
| 5 | (IPr)CuCl | 15 | — | 41% | 1 : 2 |
| **6**[f] | **$[Cu(MeCN)_4][PF_6]$** | **15** | **HMPA** | **46%** | **>20 : 1** |
| 7 | $[Cu(MeCN)_4][PF_6]$ | 15 | DMPU | 32% | 4 : 1 |
| 8 | $[Cu(MeCN)_4][PF_6]$ | 15 | TMEDA | 23% | 4 : 1 |
| 9 | $[Cu(MeCN)_4][PF_6]$ | 7.5 | HMPA | 23% | >20 : 1 |
| 10 | $[Cu(MeCN)_4][PF_6]$ | 30 | HMPA | 41% | >20 : 1 |

[a] Standard reaction conditions: epoxide (0.1 mmol, 1.0 equiv.), LHMDS (0.1 mmol, 1.0 equiv.), $PhNTf_2$ (0.1 mmol, 1.0 equiv.), −78 → 0 °C, 5 min; then add a solution of MeMgBr (0.3 mmol, 3.0 equiv.), [Cu] ($X$ mol%), and additive, 0 °C, 1 h. [b] mol% with respect to epoxide starting material. [c] Additives included at 5.0 equiv. [d] Isolated yield of **12** after column chromatography. [e] Determined by $^1H$ NMR of the crude reaction mixture. [f] Reaction performed using 1.0 mmol of epoxide.

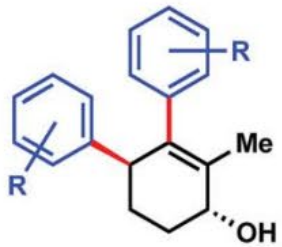
# Quick Assembling of Quassinoid Architecture



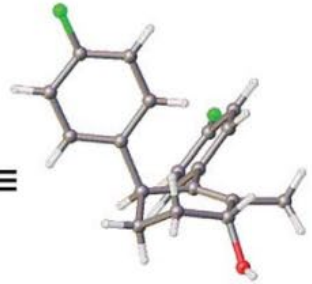

A



12, 46%

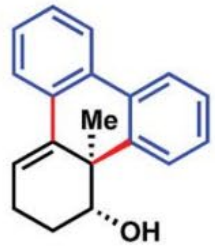


**13**, 46%, R = H
**14**, 52%, R = *p*-OMe
**15**, 44%, R = *m*-OMe
**16**, 44%, R = *p*-Me
**17**, 42%, R = *m*-Me[b]
**18**, 43%, R = F



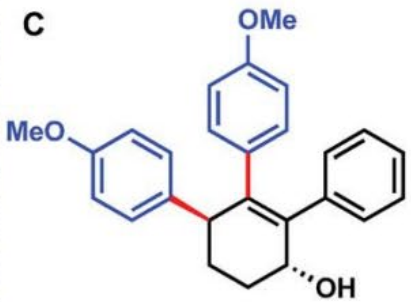
**18**, [X-ray]

B

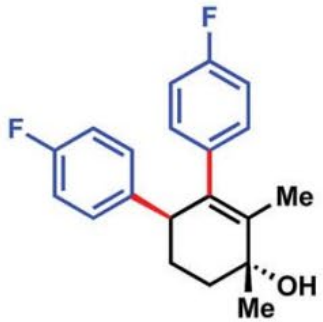


**22**, 34%[c,d]

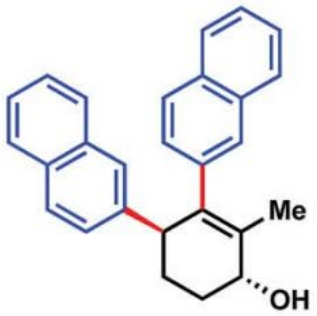
C



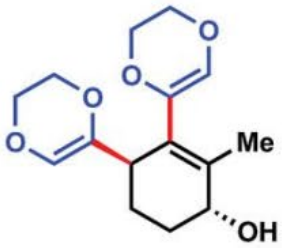
**24**, 40%



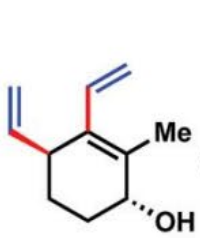
**25**, (54%)[e]



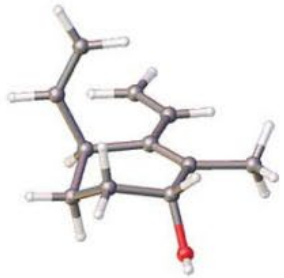
**19**, 40%



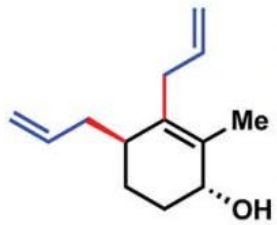
**20**, 55%



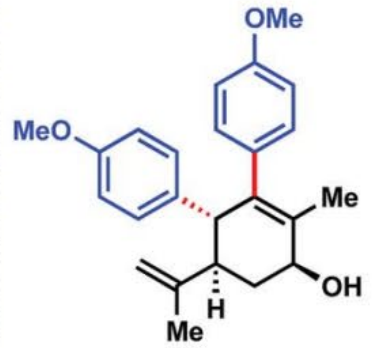
**21**, 35%



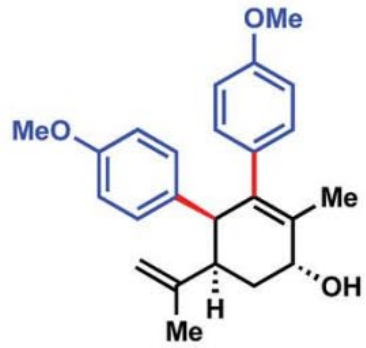
[X-ray]



**23**, 58%[c]
(1:1 d.r.)



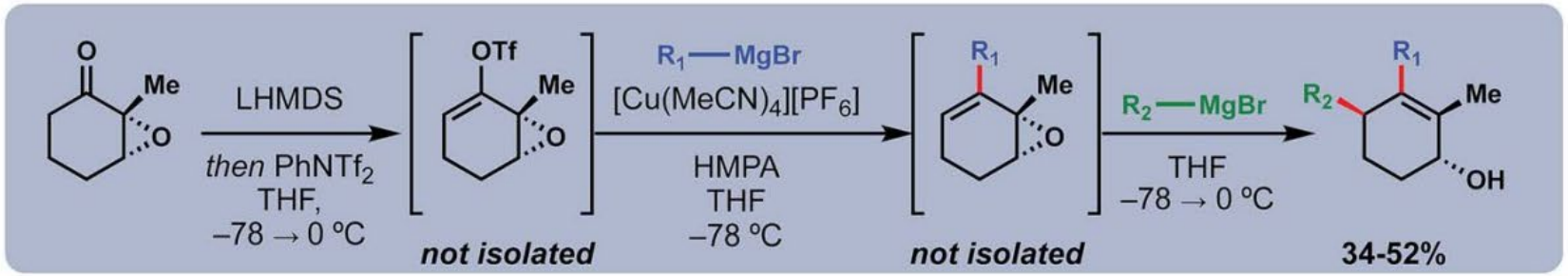
**26**, 52%



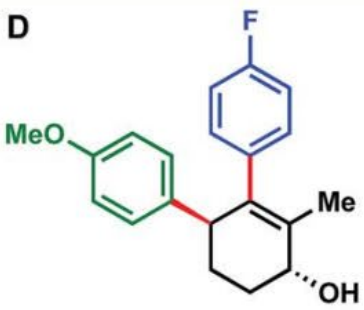
**27**, 51%[f]

M. L. Condakes, R. Z. Rosen, S. J. Harwood and T. J. Maimone. *Chem. Sci.,* **2019**, *10*, 768–772.

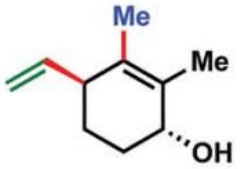
# Quick Assembling of Quassinoid Architecture



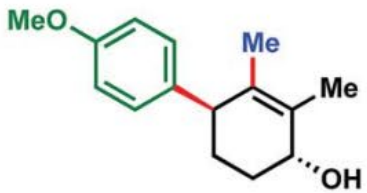

D



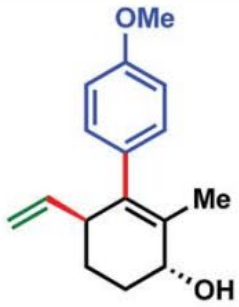
**28**, 52%



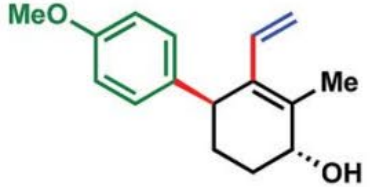
**29**, 34%



**30**, 48%

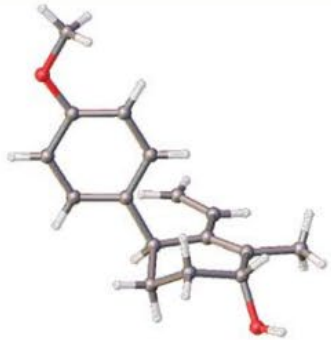


**31**, 48%



**32**, 50%

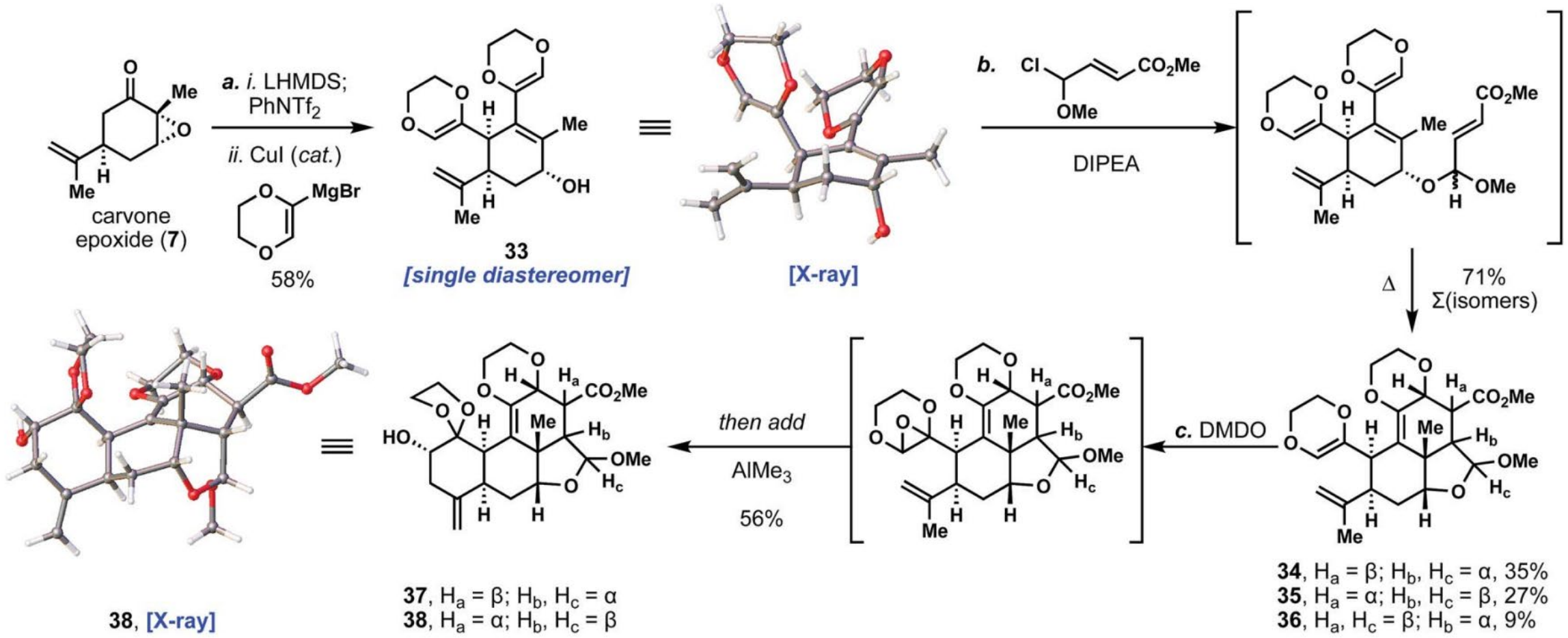
≡



[X-ray]

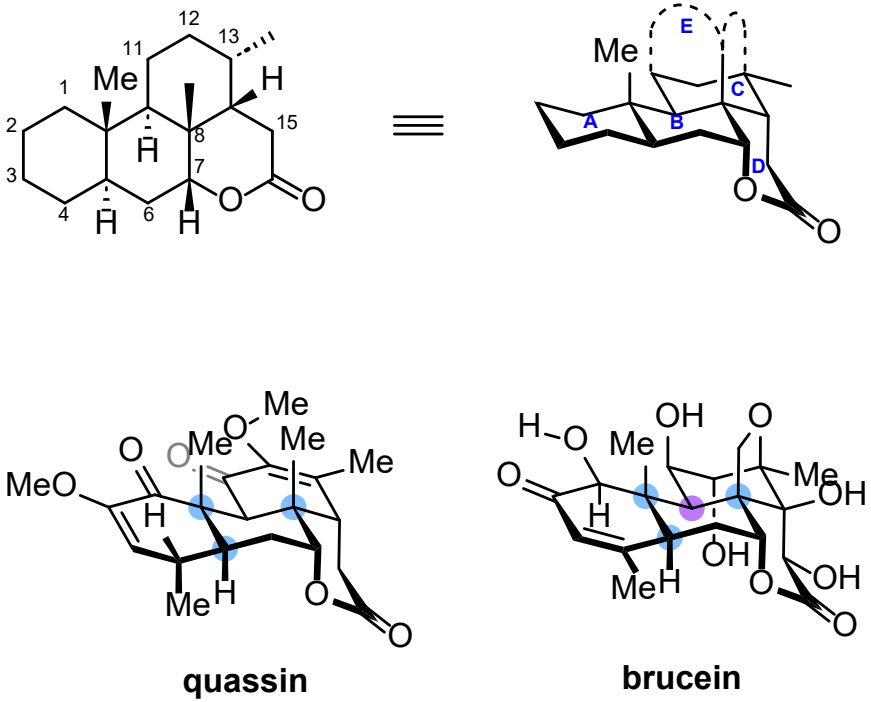
M. L. Condakes, R. Z. Rosen, S. J. Harwood and T. J. Maimone. *Chem. Sci.,* **2019**, *10*, 768–772.

# A 3-step Synthesis




M. L. Condakes, R. Z. Rosen, S. J. Harwood and T. J. Maimone. *Chem. Sci.,* **2019**, *10*, 768–772.

# Summary




**quassin** **brucein**

- Crucial Stereocenters: C5, C8, C10. C9
- Strategies:
  - “Scaffold Transformation”; C—BC—ABC—ABCD (Valenta)
  - AB(W-M ketone)—ABC—ABCD (Grieco)
  - C(carvone) —CBA—ABCD (Shing, quassin, samaderine)
  - A+C—ABC—ABCD (Pronin)
- Approaches:
  - Diels-Alder reaction
  - TM catalyzed cyclization
  - Nucleophilic reactions
  - Radical approaches (Giese, MHAT/Giese)

# Synthesis of Azadirachtin A (Ley, 2007, the Only So Far)