Synthetic Studies towards Taxol

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Peking University
Oct. 23rd, 2020

Contents

- ✓ **Introduction:** history, mechanism, classification, semi-synthesis & medicines
- ✓ **Selected strategies to construct taxane skeleton**
  - ➢ Biosynthesis & biomimetic synthesis
  - ➢ Diels-Alder
  - ➢ Miscellaneous
- ✓ **Total synthesis of taxol**
- ✓ **Summary**

History

National Cancer Institute (NCI)
US, 1950s

extract from the bark of *T. brevifolia* Nutt.
KB (人口腔表皮样癌细胞) cytotoxicity
1964

isolation (0.014%)
Monroe Wall
Mansukh Wani
1966

structure determined by NMR
1971

mechanism of action
first compound to promote
the microtubules assembly
1979

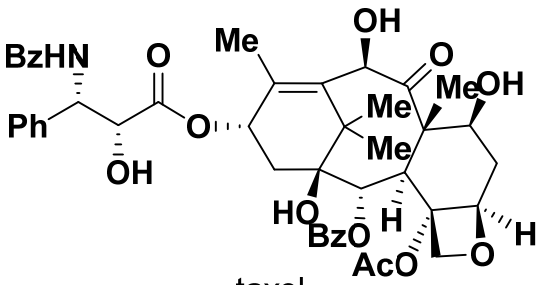
Phases I/II/III
1980s

semi-synthesis
1988

refractory ovarian cancer
FDA, 1992

total synthesis
1994

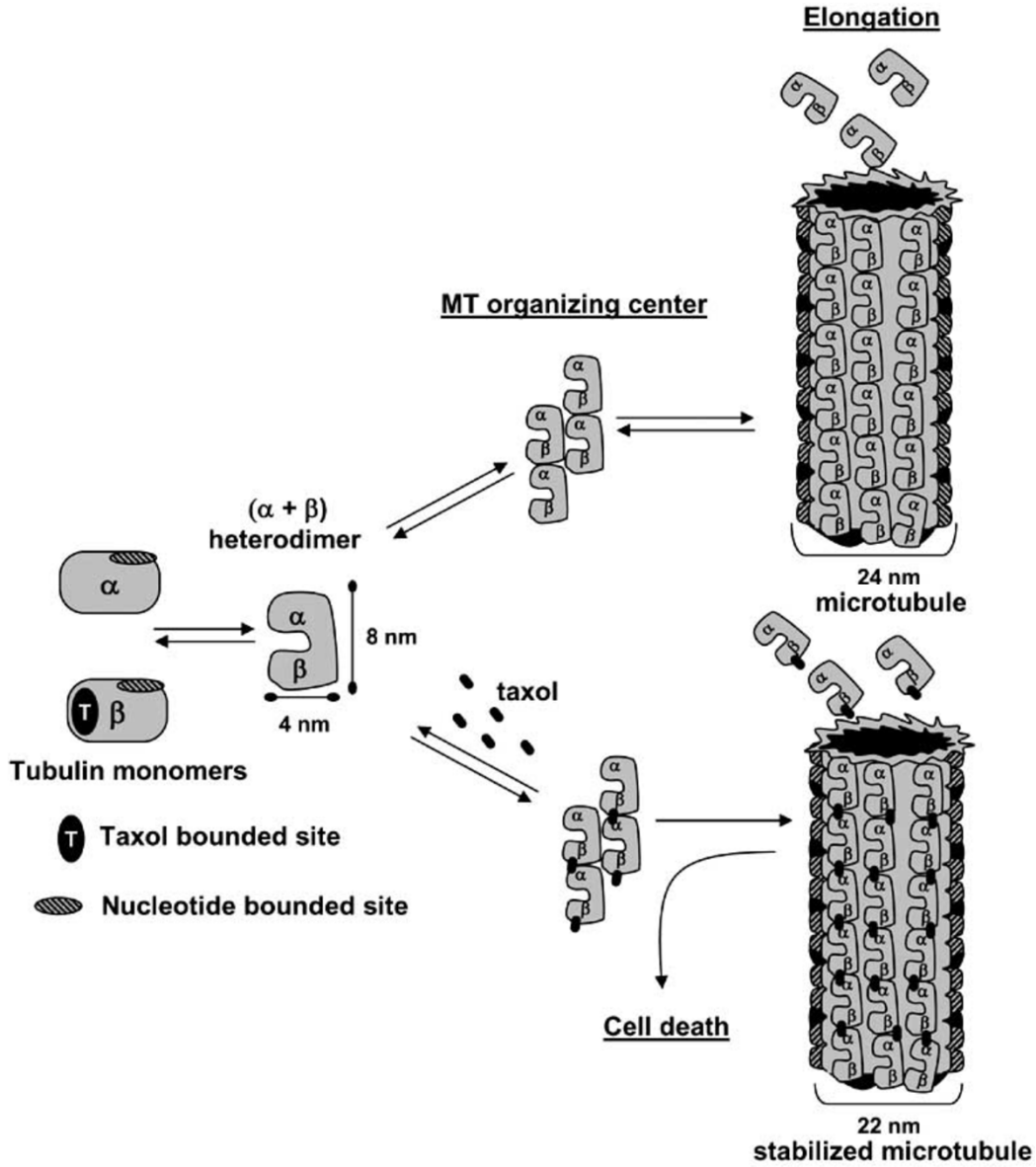
plant cell fermentation (PCF)
metric ton scale
1996



taxol

Oberlies, N. H.; Kroll, D. J. *J. Nat. Prod.* **2004**, *67*, 129.
Wang, Y.-F.; Shi, Q.-W.; Dong, M.; Kiyota, H.; Gu, Y.-C.; Cong, B. *Chem. Rev.* **2011**, *111*, 7652.

Mechanism of action



Expósito, O.; Bonfill, M.; Moyano, E.; Onrubia, M.; Mirjalili, M. H.; Cusidó, R. M.; Palazón, J. *Anti-Cancer Agents in Medicinal Chemistry* **2009**, *9*, 109.

Classification

National Cancer Institute (NCI)
US, 1950s

isolation (0.014%)
Monroe Wall
Mansukh Wani
1966

mechanism of action
first compound to promote
the microtubules assembly
1979

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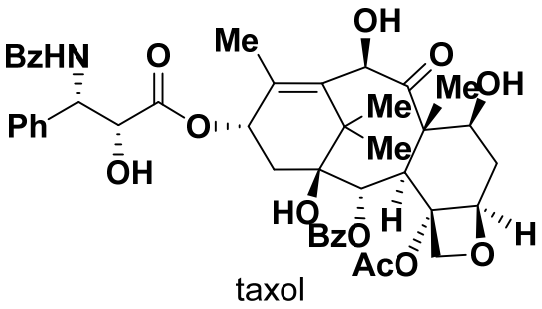
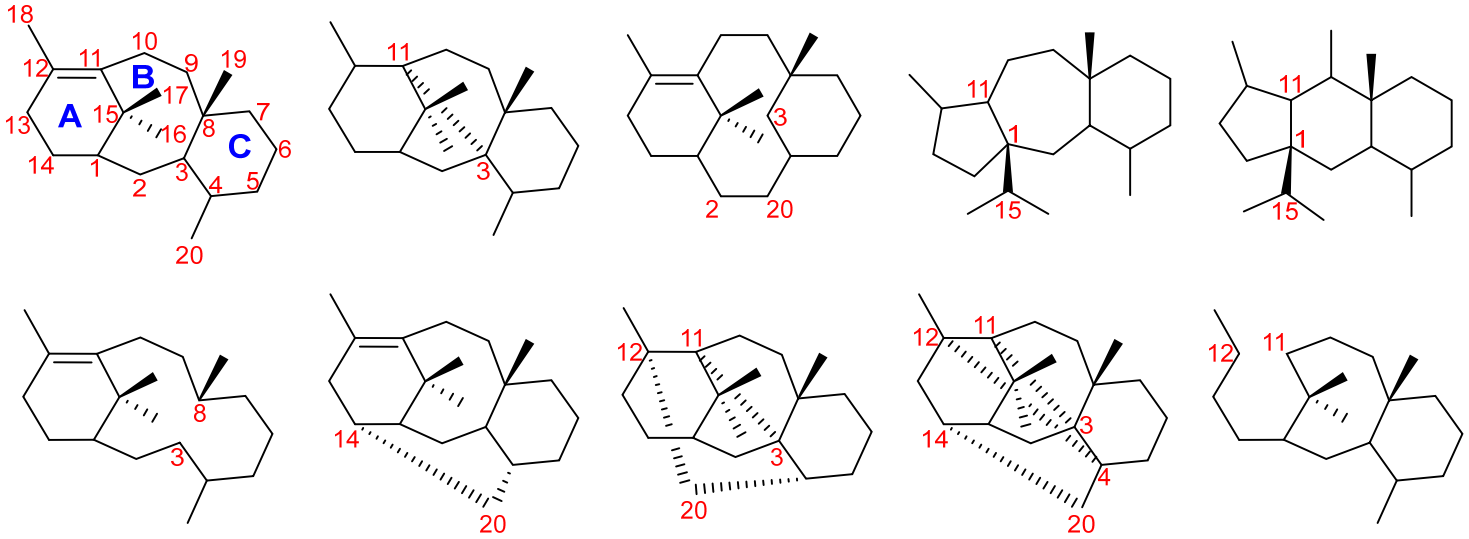
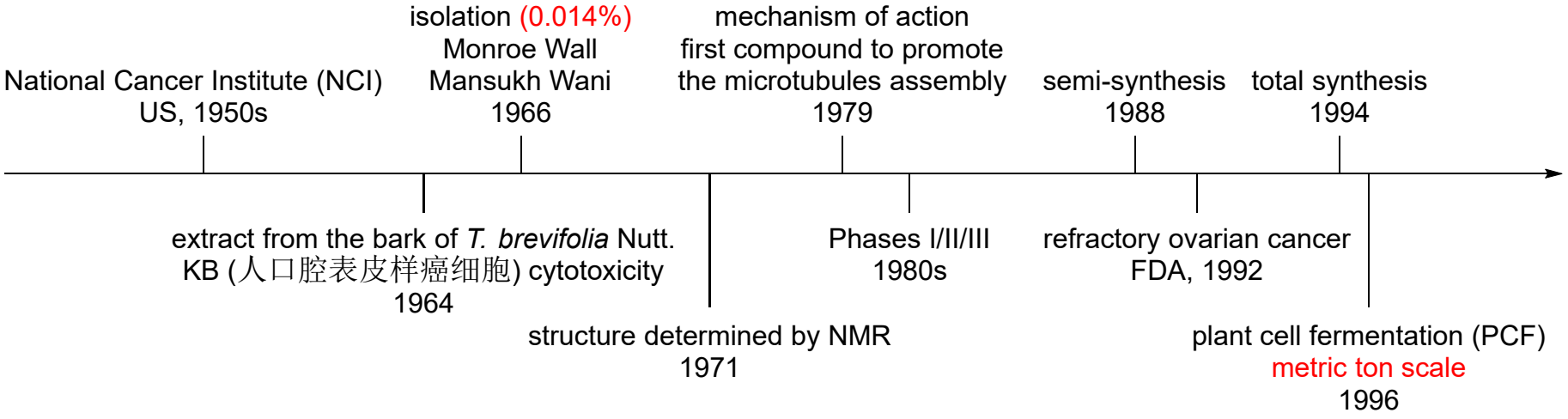


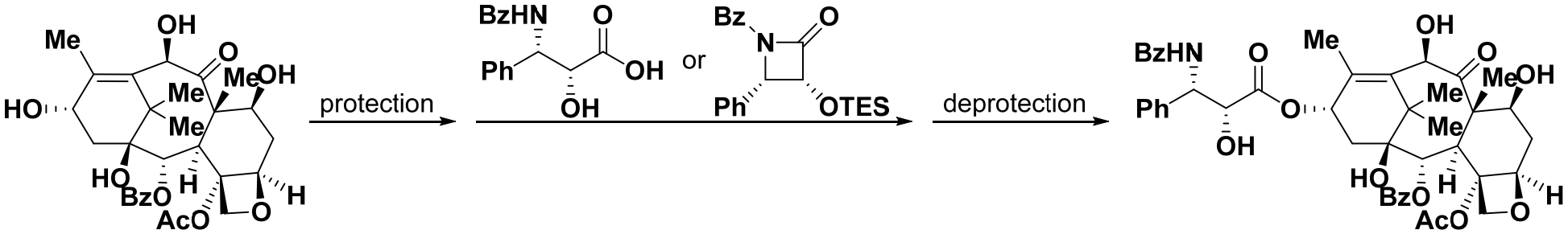
taxol



Oberlies, N. H.; Kroll, D. J. *J. Nat. Prod.* **2004**, *67*, 129.
Wang, Y.-F.; Shi, Q.-W.; Dong, M.; Kiyota, H.; Gu, Y.-C.; Cong, B. *Chem. Rev.* **2011**, *111*, 7652.

Semi-synthesis



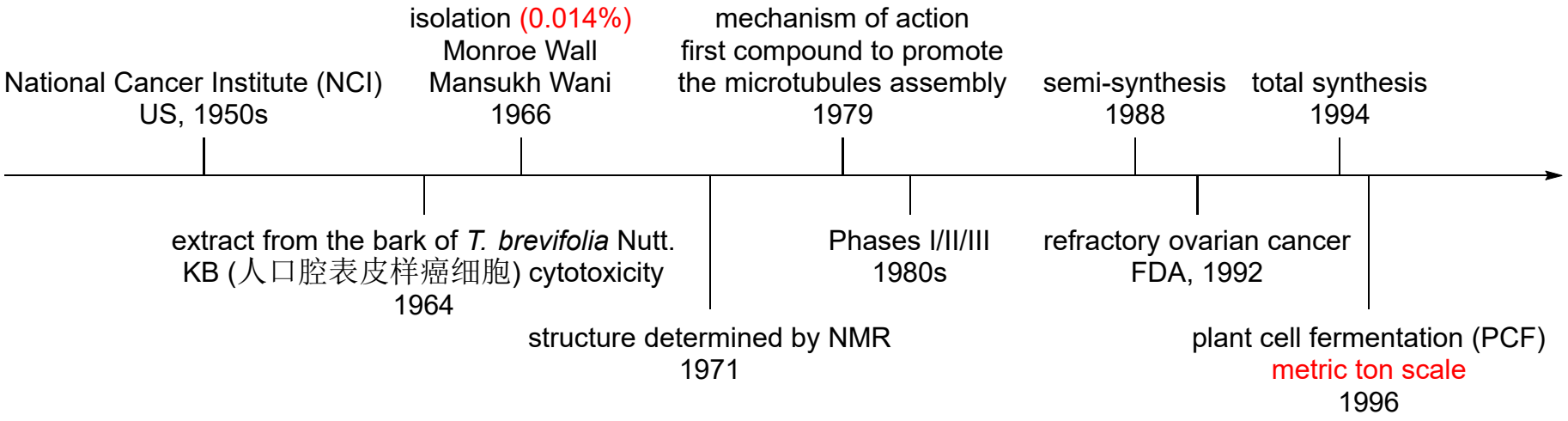


10-deacetyl baccatin III (10-DAB)
from a renewable source
(1g/kg in 1988)

taxol

Oberlies, N. H.; Kroll, D. J. *J. Nat. Prod.* **2004**, *67*, 129.
Wang, Y.-F.; Shi, Q.-W.; Dong, M.; Kiyota, H.; Gu, Y.-C.; Cong, B. *Chem. Rev.* **2011**, *111*, 7652.
Denis, J.-N.; Greene, A. E. *J. Am. Chem. Soc.* **1988**, *110*, 5917.
Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985.

Medicines



商品名	公司	上市时间	技术
Lipusu	Luye Pharma	2003/01 中国	Liposome
Abraxane	Celgene	2005/02 美国 2008/01 中国	Albumin-bound Nanoparticle
Cynviloq	Samyang	2007/01 韩国 2012/12 印度	Polymeric Micelle
Nanoxel	Fresenius Kabi	2007/01 印度	Nanoparticle
PICN	Sun Pharma	2014/05 印度	Nanoparticle
Apealea/Paclical	Oasmia	2015/10 俄罗斯联邦	XR-17 Encapsulated Micelle

Oberlies, N. H.; Kroll, D. J. *J. Nat. Prod.* **2004**, *67*, 129.
Wang, Y.-F.; Shi, Q.-W.; Dong, M.; Kiyota, H.; Gu, Y.-C.; Cong, B. *Chem. Rev.* **2011**, *111*, 7652.

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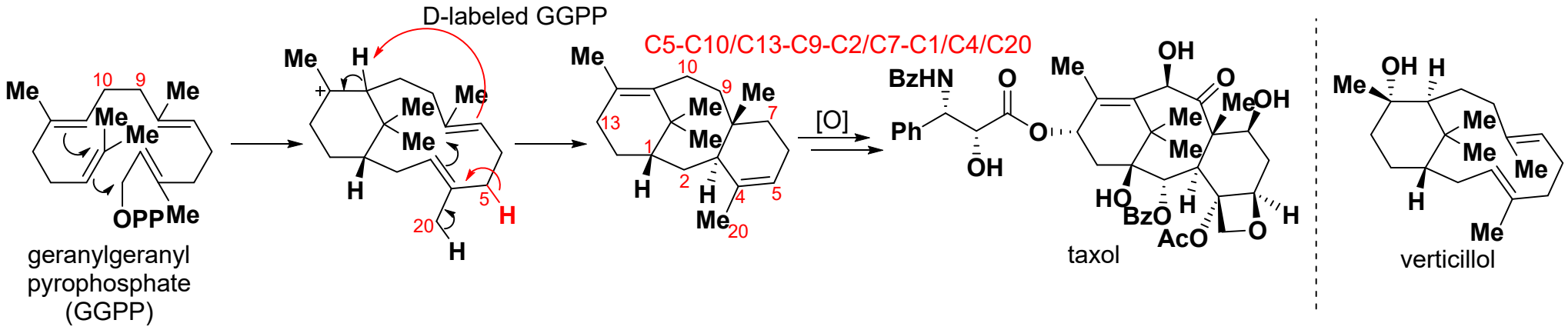
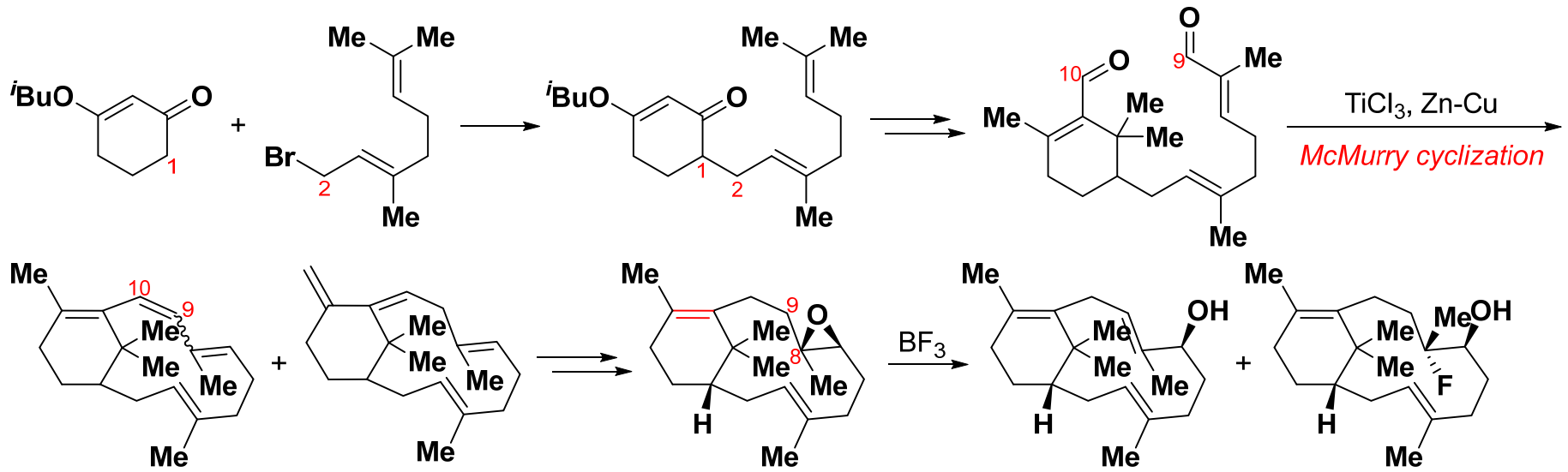
  - ➢ Miscellaneous

- ✓ **Total synthesis of taxol**

- ✓ **Summary**

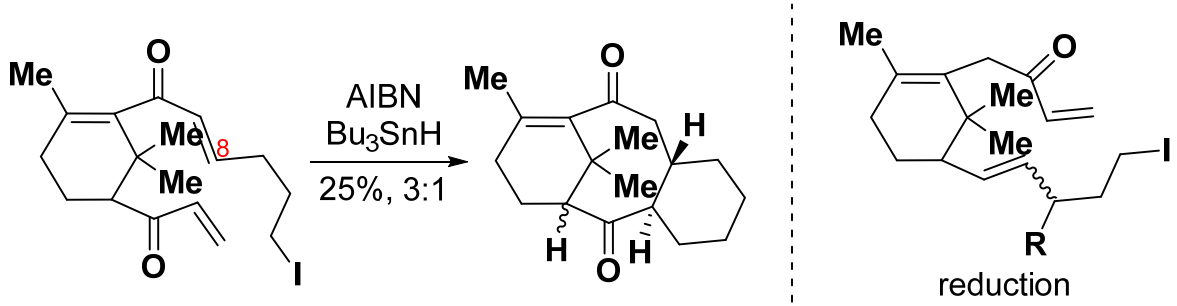
Biosynthesis & biomimetic synthesis

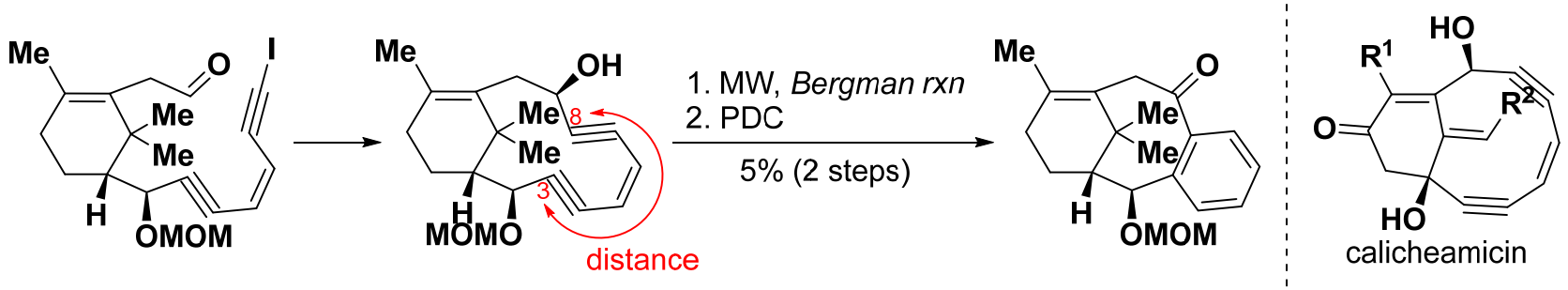




Williams, D. C.; Carroll, B. J.; Jin, Q.; Rithner, C. D.; Lenger, S. R.; Floss, H. G.; Coates, R. M.; Williams, R. M.; Croteau, R. *Chem. Bio.* **2000**, *7*, 969. Expósito, O.; Bonfill, M.; Moyano, E.; Onrubia, M.; Mirjalili, M. H.; Cusidó, R. M.; Palazón, J. *Anti-Cancer Agents in Medicinal Chemistry* **2009**, *9*, 109. Jackson, C. B.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 3393. Begley, M. J.; Jackson, C. B.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 3397.

Biomimetic synthesis



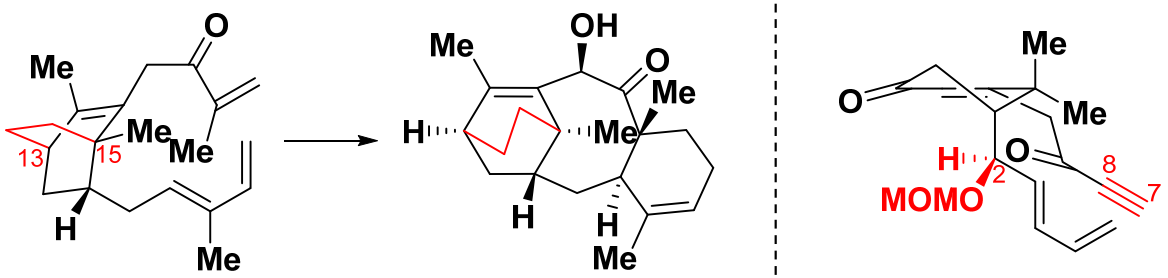


Cyclase phase

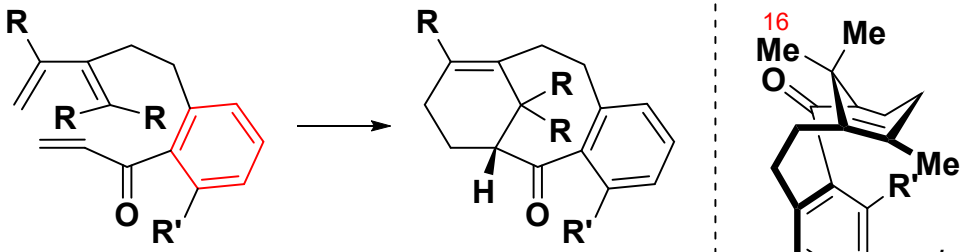
Hitchccck, S. A.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4843. Houldsworth, S. J.; Pattenden, G.; Pryde, D. C.; Thomson, N. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1091. Hitchccck, S. A.; Houldsworth, S. J.; Pattenden, G.; Pryde, D. C.; Thomson, N. M.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3181. Goldring, W. P. D .; Pattenden, G.; Rimmington, S. L. *Tetrahedron* 10 **2009**, *65*, 6670. Lu, Y.-F.; Harwig, C. W.; Fallis, A. G. *Can. J. Chem.* **1995**, *73*, 2253.

Diels-Alder

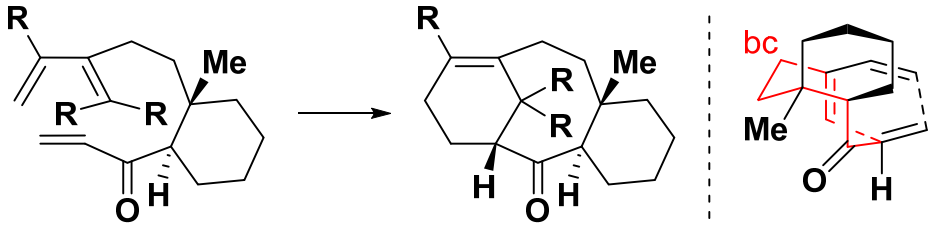
- Construction of C ring



- Construction of A ring



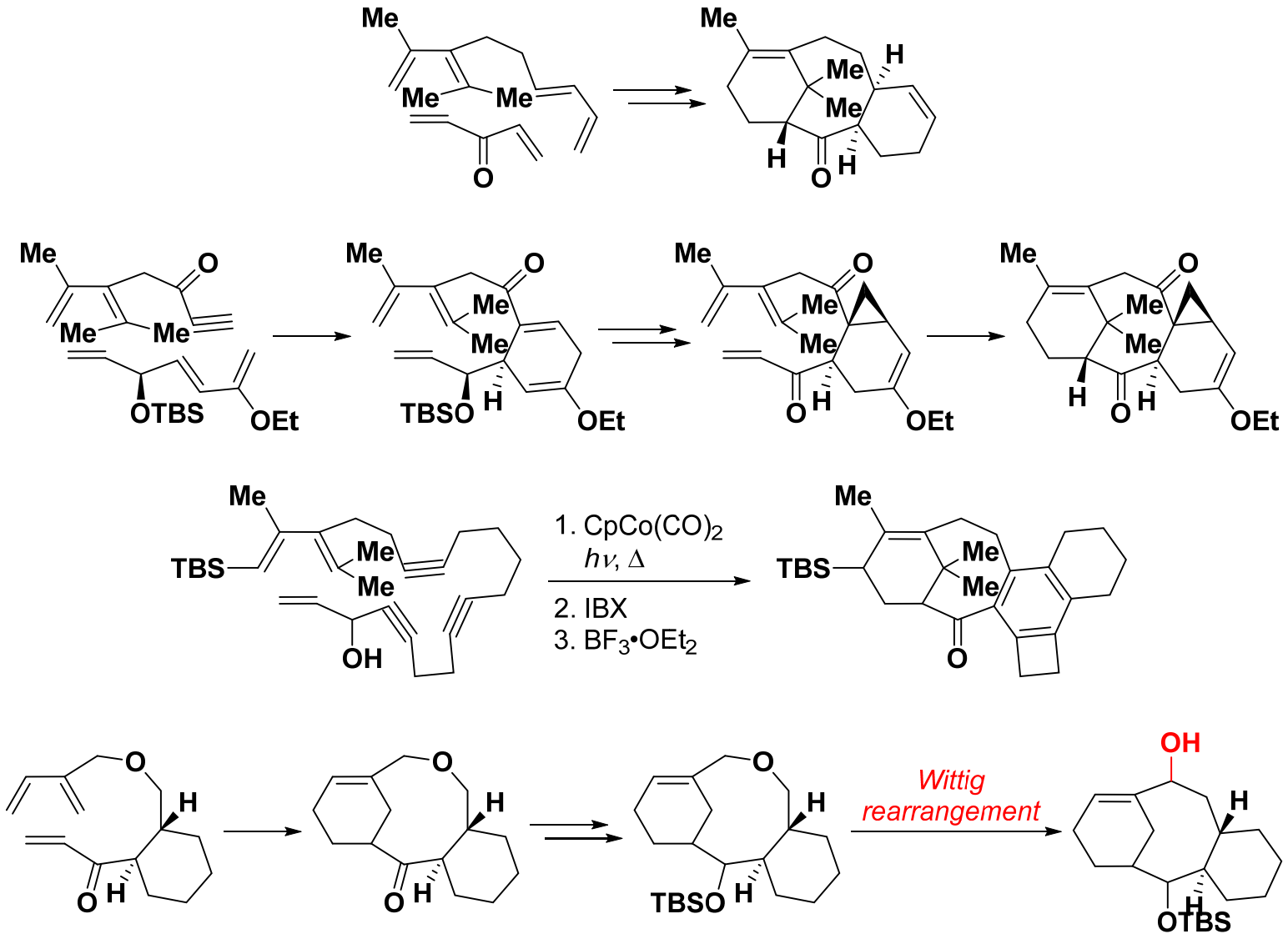
R = H, Me; R' = H, OMe



R = H, Me

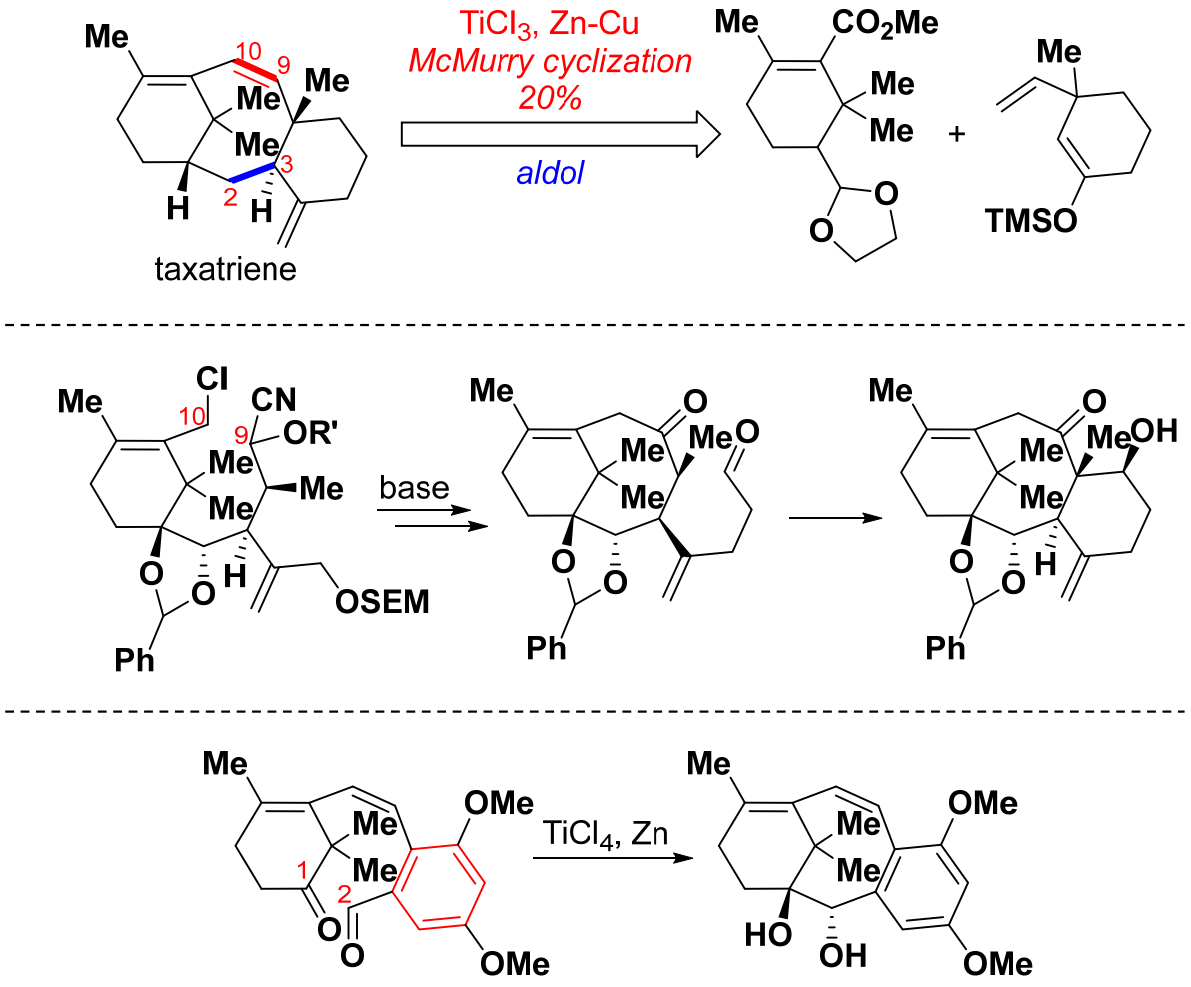
Sakan, K.; Craven, B. *J. Am. Chem. Soc.* **1983**, *105*, 3732.
Lu, Y.-F.; Fallis, A. G. *Tetrahedron Lett.* **1993**, *34*, 3367.
Shea, K. J.; Davis, P. D. *J. Am. Chem. Soc.* **1986**, *108*, 4953.
M. Brown, P. A.; Jenkins, P. R.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Chem. Commun.* **1984**, 253.

Diels-Alder



Winkler, J. D.; Kim, H. S.;Kim, S. *Tetrahedron Lett.* **1995**, *36*, 687.
Winkler, J. D.; Holland, J. M.; Peters, D. A. *J. Org. Chem.* **1996**, *61*, 9074.
Chouraqui, G.; Petit, M.; Phansavath, P.; Aubert, C.; Malacria, M. *Eur. J. Org. Chem.* **2006**, 1413.
Yadav, J. S.; Ravishankar, R. *Tetrahedron Lett.* **1991**, *32*, 2629.

Miscellaneous



Kende, A.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513. Stork, G.; Manabe, K.; Liu, L. *J. Am. Chem. Soc.* **1998**, *120*, 1337. Swindell, C. S.; Chander, M. C.; Heerding, J. M.; Klimko, P. G.; Rahman, L. T.; Raman, J. V.; Venkataraman, H. *Tetrahedron Lett*. **1993**, *34*, 7005.

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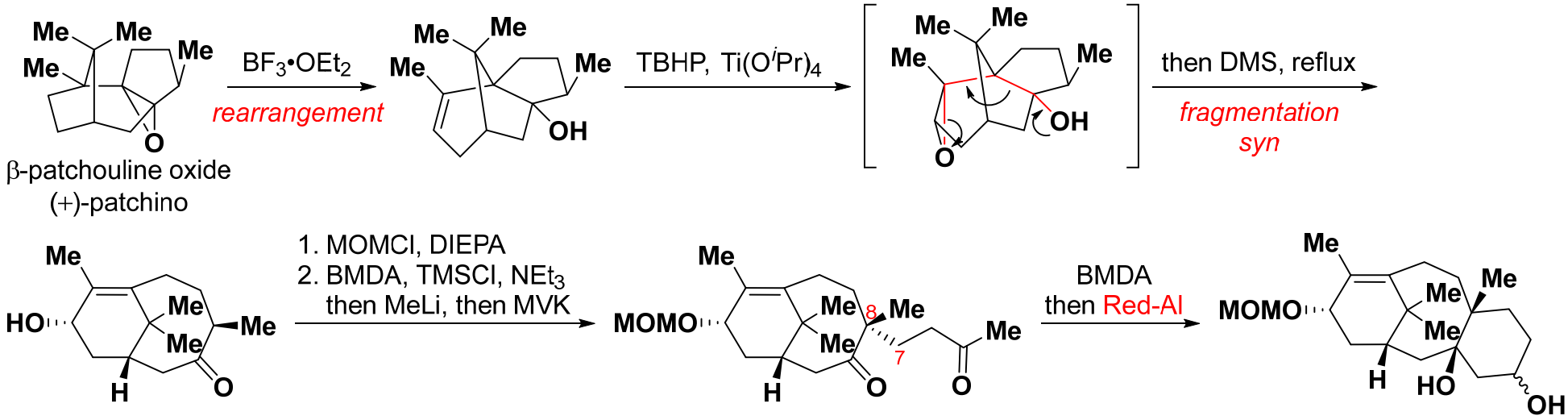
- ✓ **Summary**

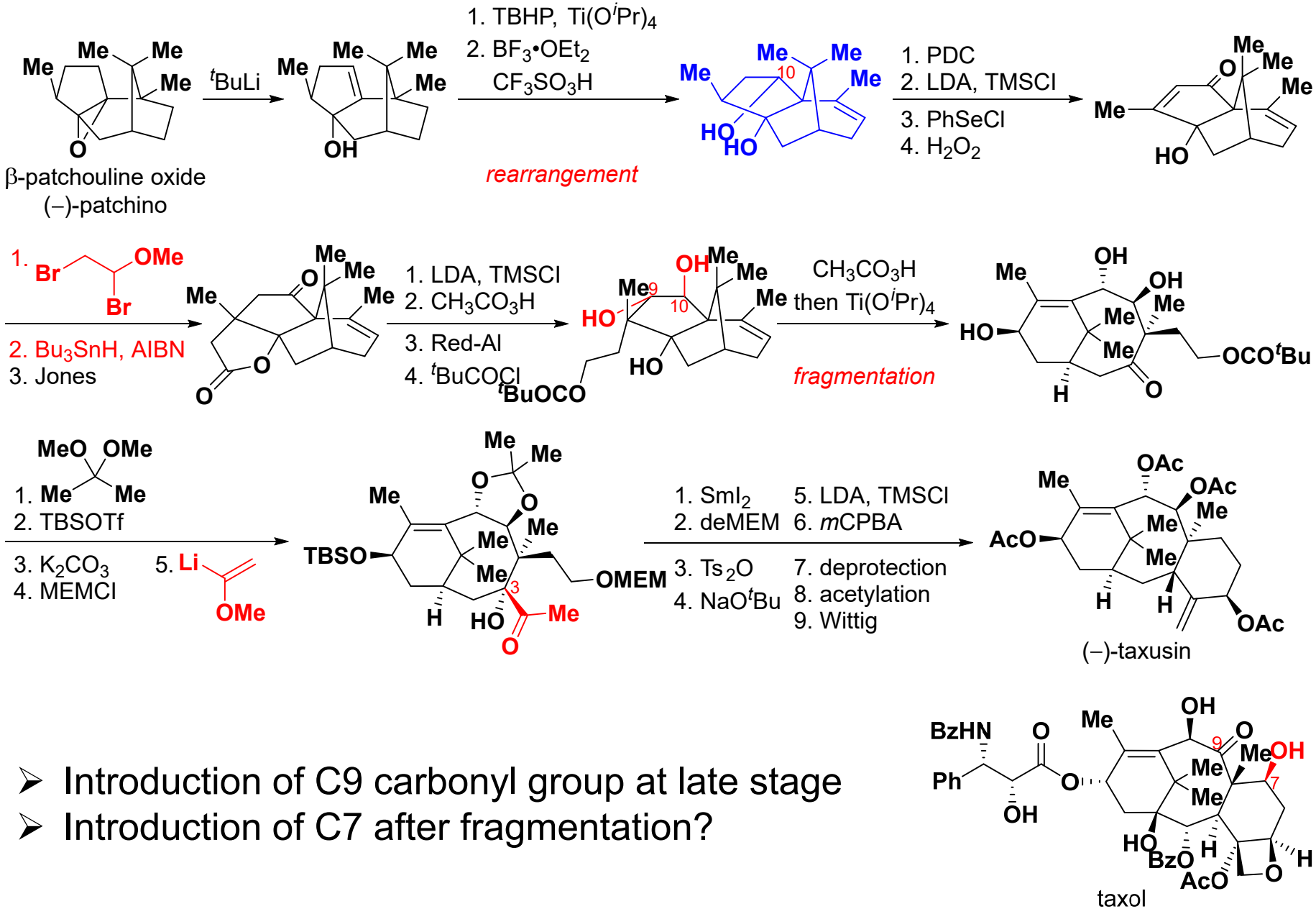
Holton's work



- Fragmentation strategy
- Introduction of C7 before fragmentation
- Construction of C ring via aldol condensation?

Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731.

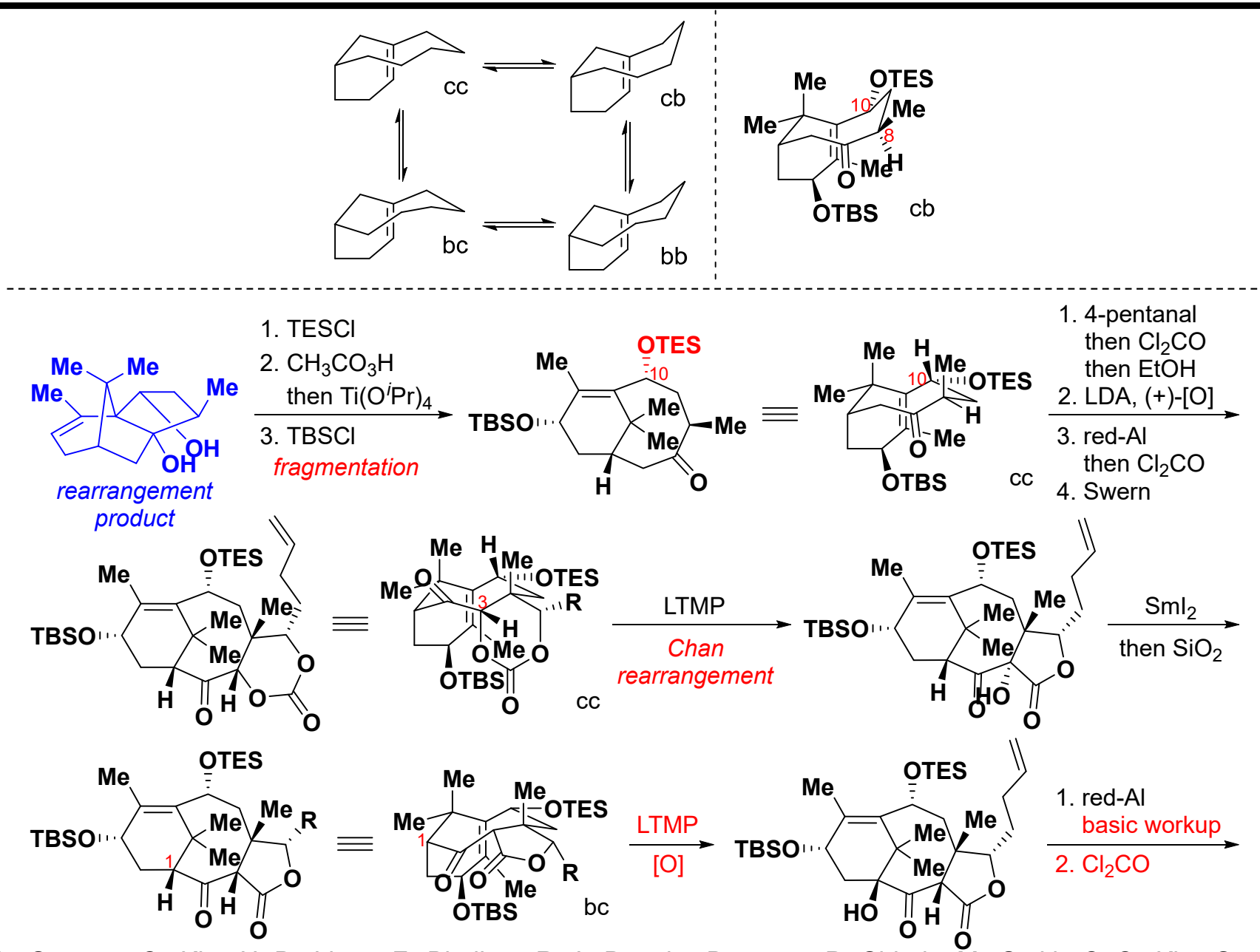
Holton's work



- Introduction of C9 carbonyl group at late stage
- Introduction of C7 after fragmentation?

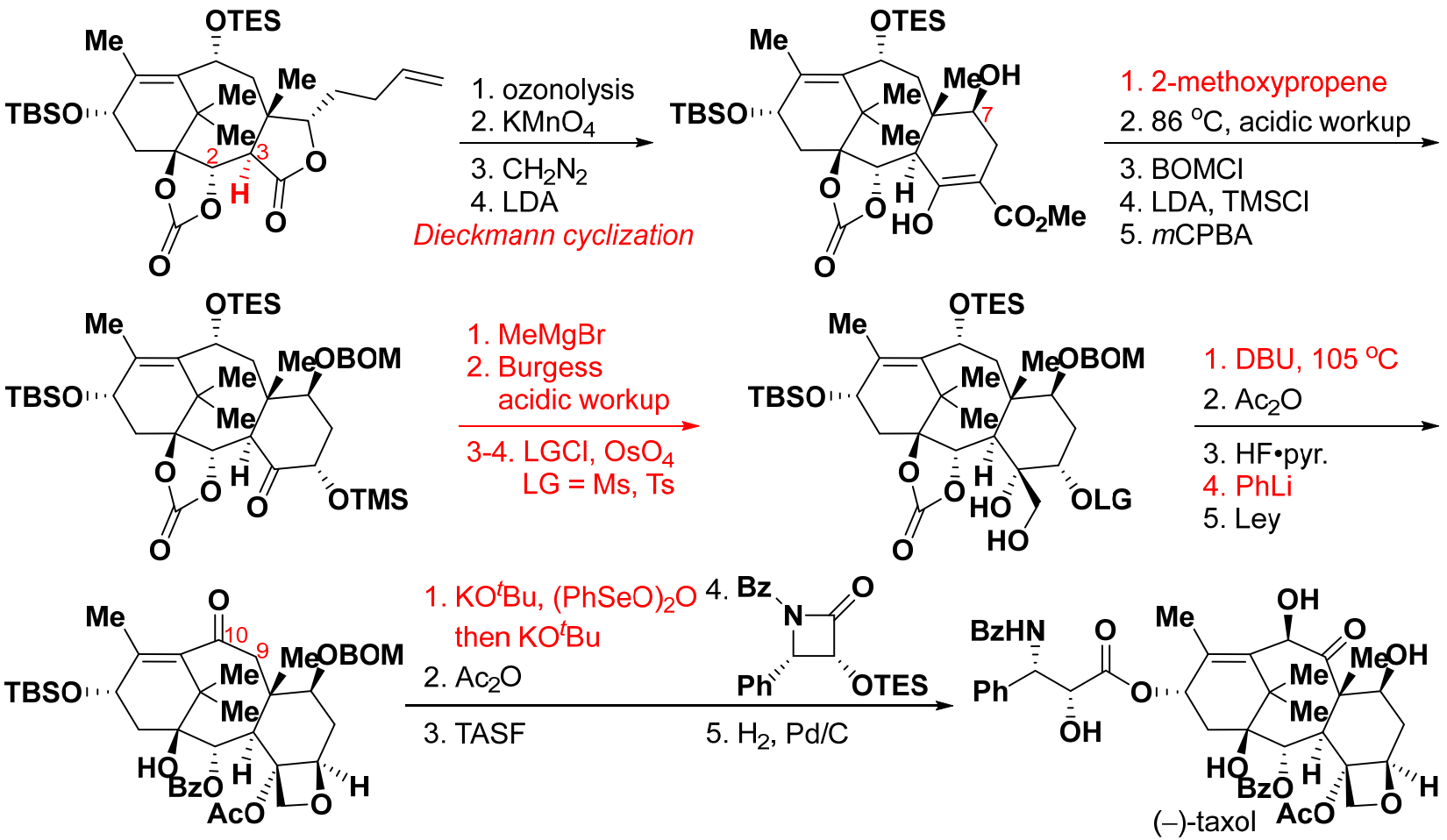
Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.

Holton's work



Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Douglas Boatman, P.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597.

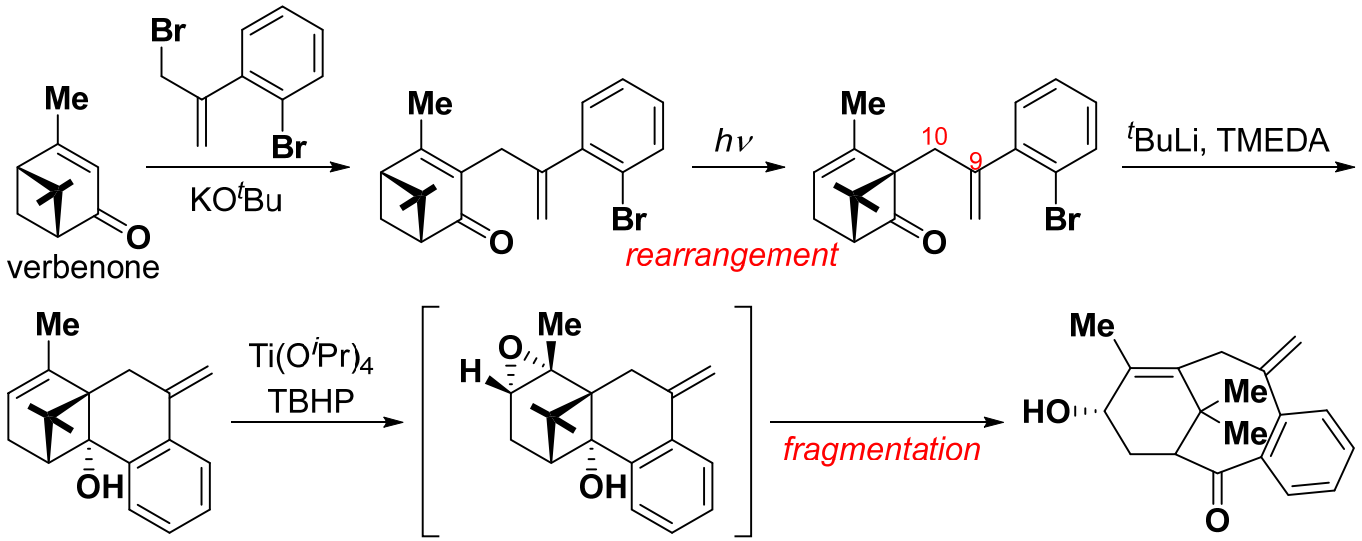
Holton's work



- Chiral pool
- Fragmentation strategy
- Conformation control
- C1 C9 oxidation via enolate
- C1 C2 protection
- Construction of D ring
- Oxidative dance for C9 C10

Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Douglas Boatman, P.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. *J. Am. Chem. Soc.* **1994**, *116*, 1599.

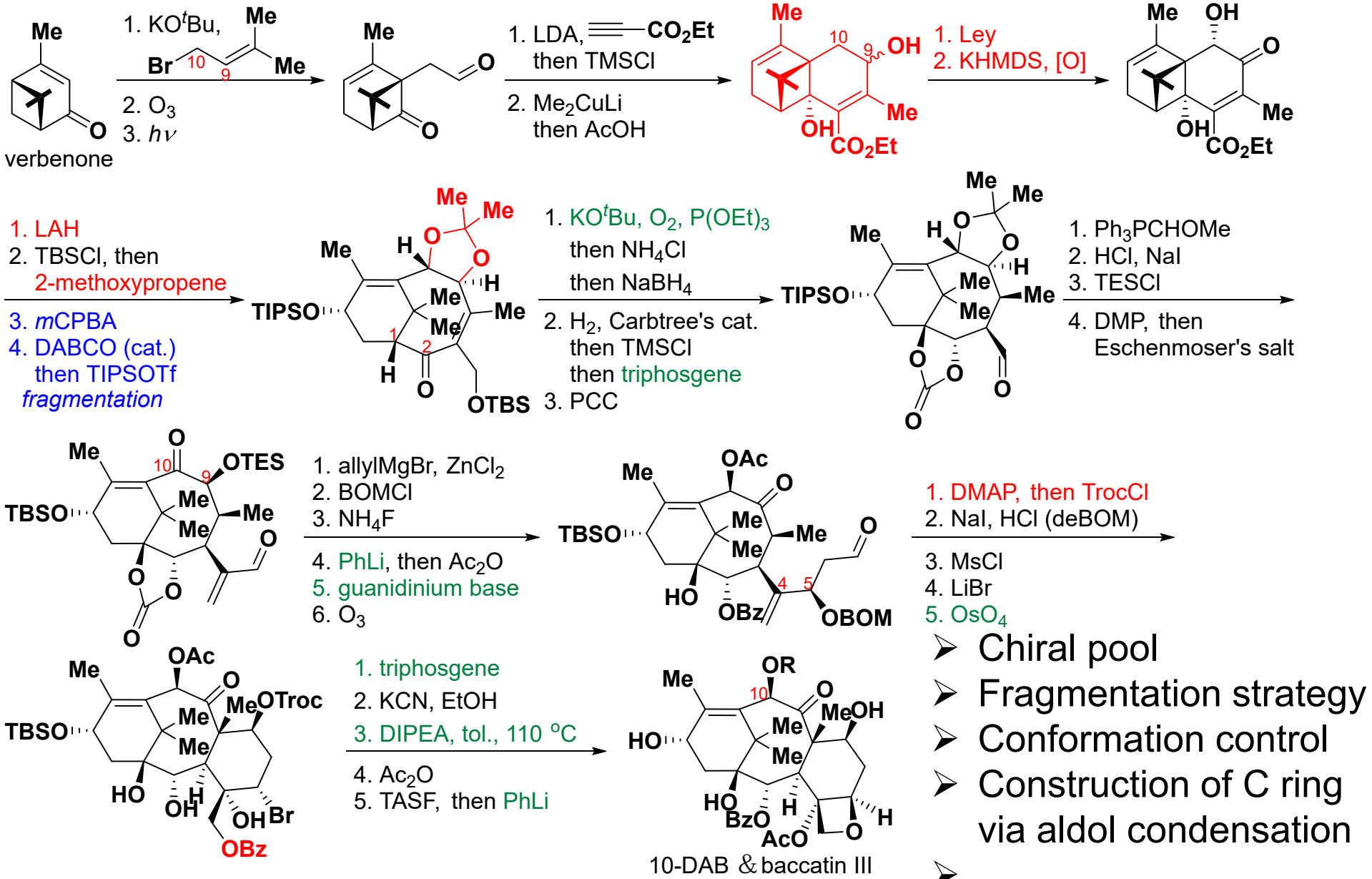
Wender's work



- Fragmentation strategy
- Compatibility of the C ring subunit with the photochemical conditions
- Introduction of a C9 C10 linker

Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878.

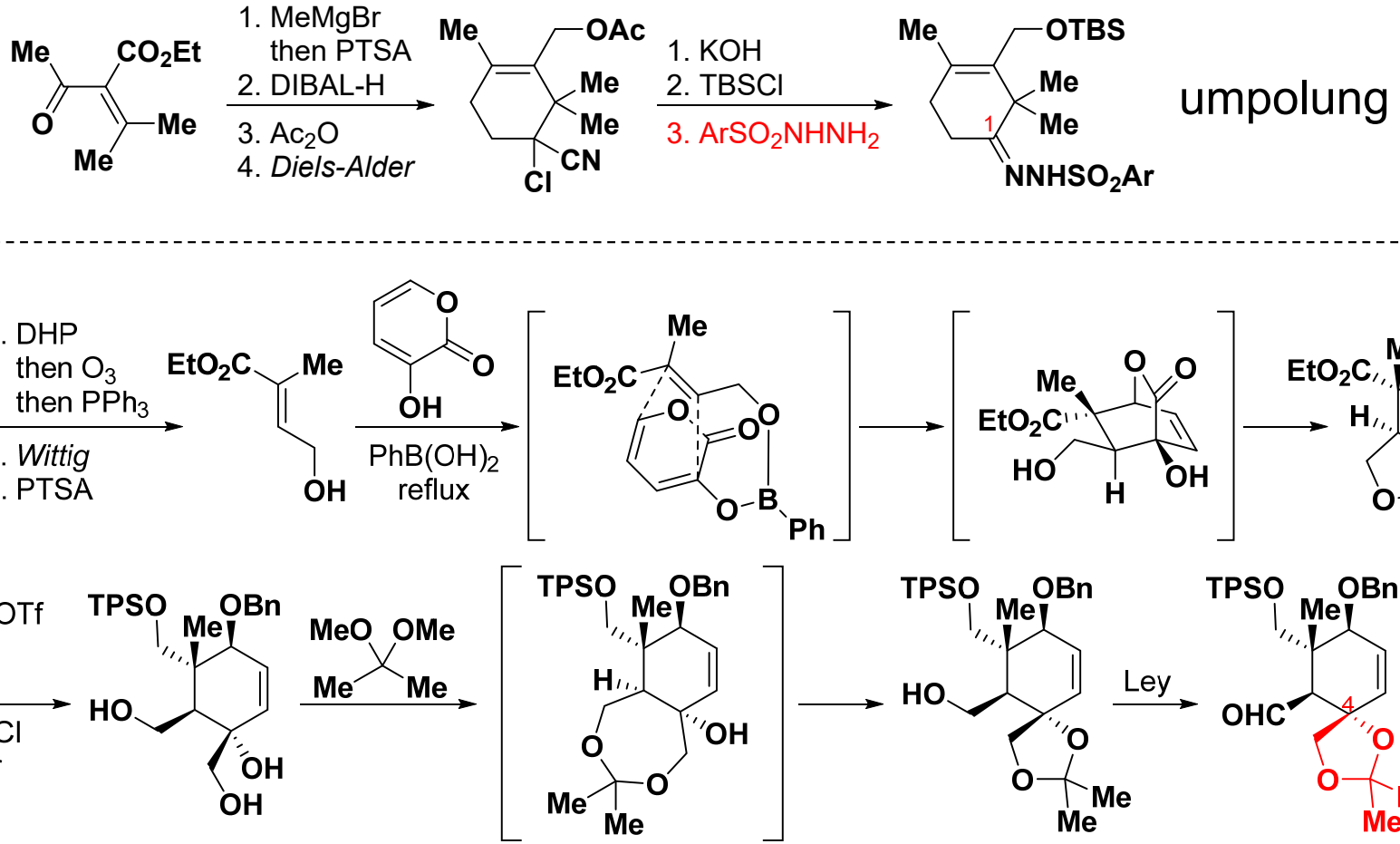
Wender's work



- Chiral pool
- Fragmentation strategy
- Conformation control
- Construction of C ring via aldol condensation
- .....

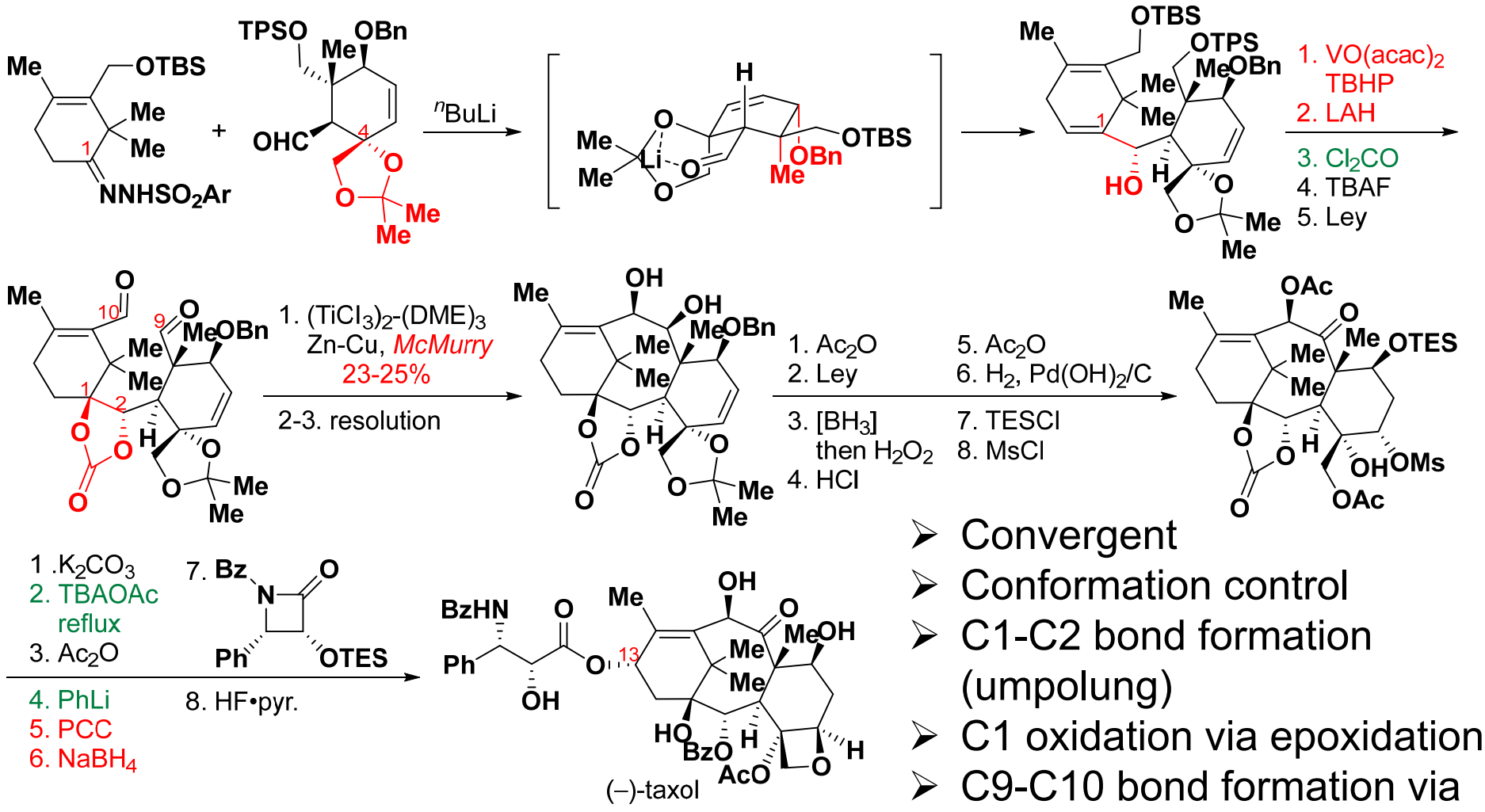
Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Gränicher, C.; Houze, J. B.; Jänichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K.;; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L. *J. Am. Chem. Soc.* **1997**, *119*, 2755. *J. Am. Chem. Soc.* **1997**, *119*, 2757.

Nicolaou's work



Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630.

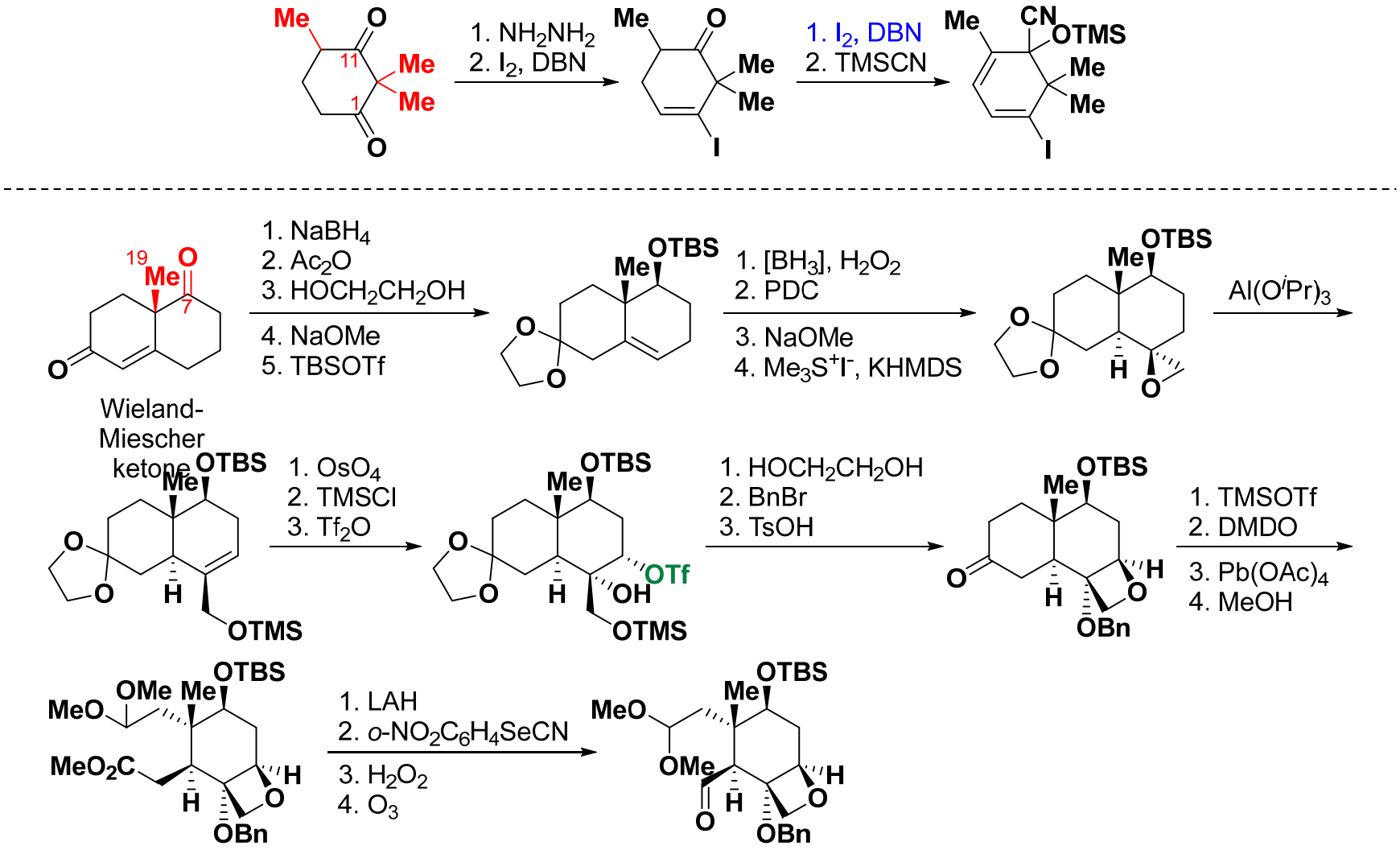
Nicolaou's work



- Convergent
- Conformation control
- C1-C2 bond formation (umpolung)
- C1 oxidation via epoxidation
- C9-C10 bond formation via McMurry cyclization
- C13 oxidation via PCC
- ……

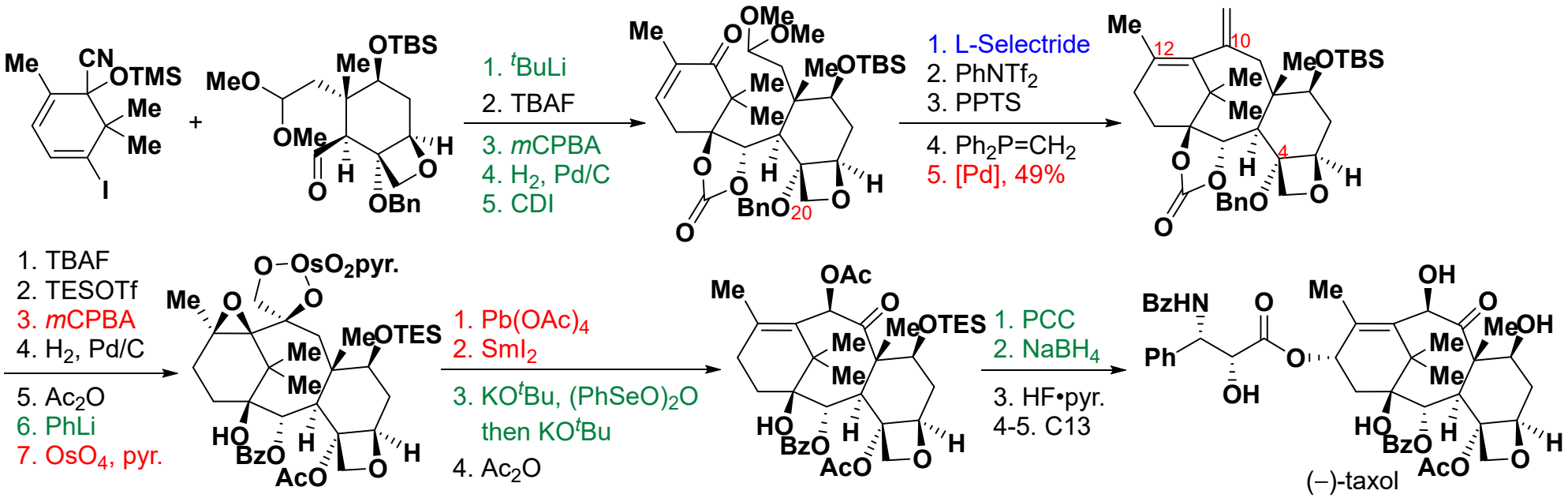
Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630.

Danishefsky's work



Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link,J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843.

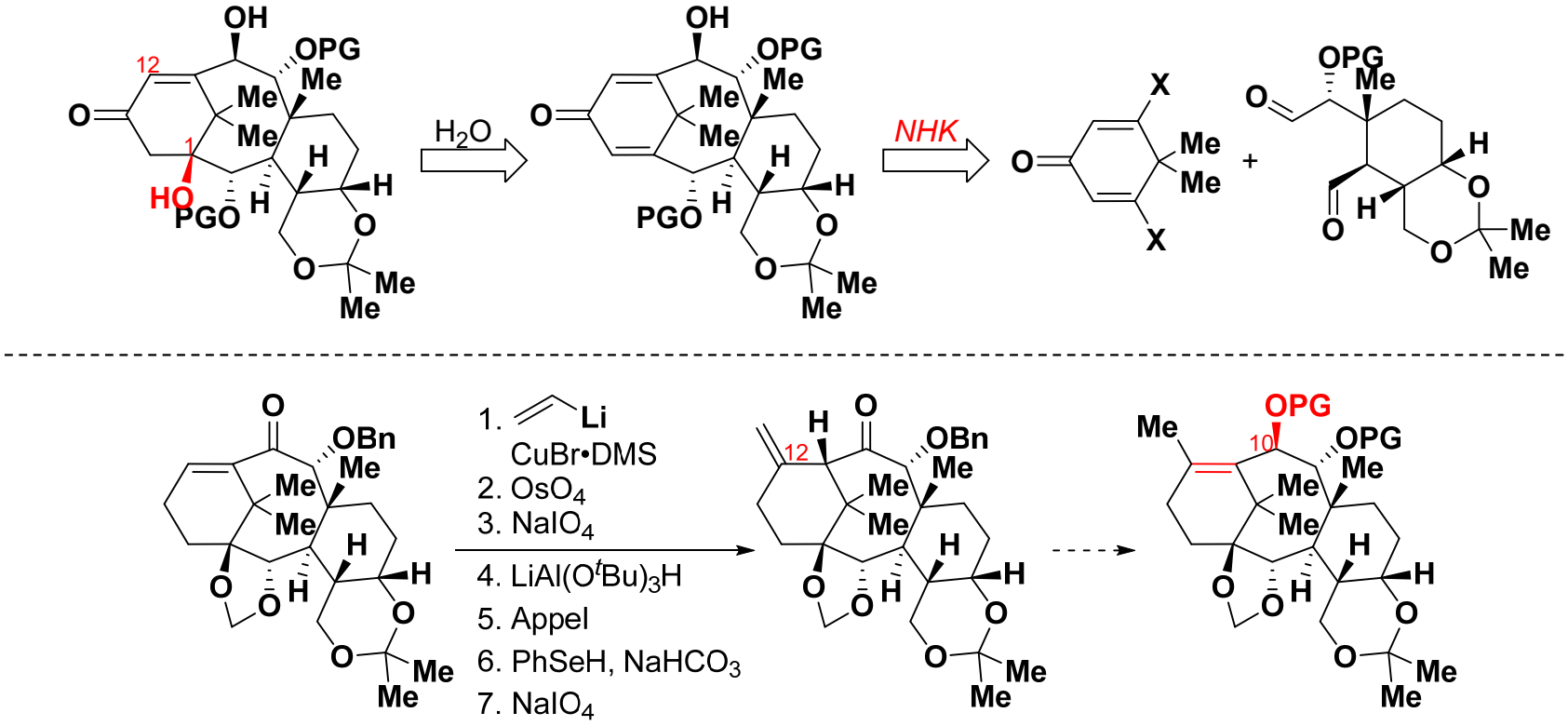
Danishefsky's work

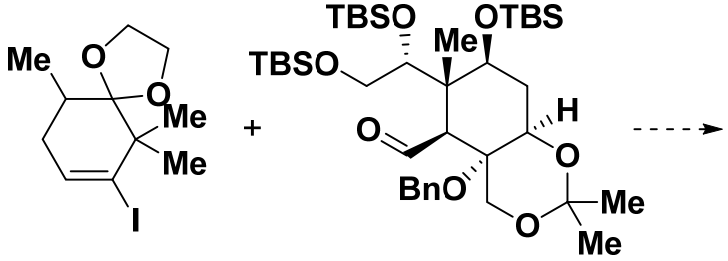


- Convergent
- Chiral pool
- SM selection
- Construction of D ring at early stage
- C10-C11 bond formation via palladium chemistry
- ……

Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link,J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843.

Kishi's work

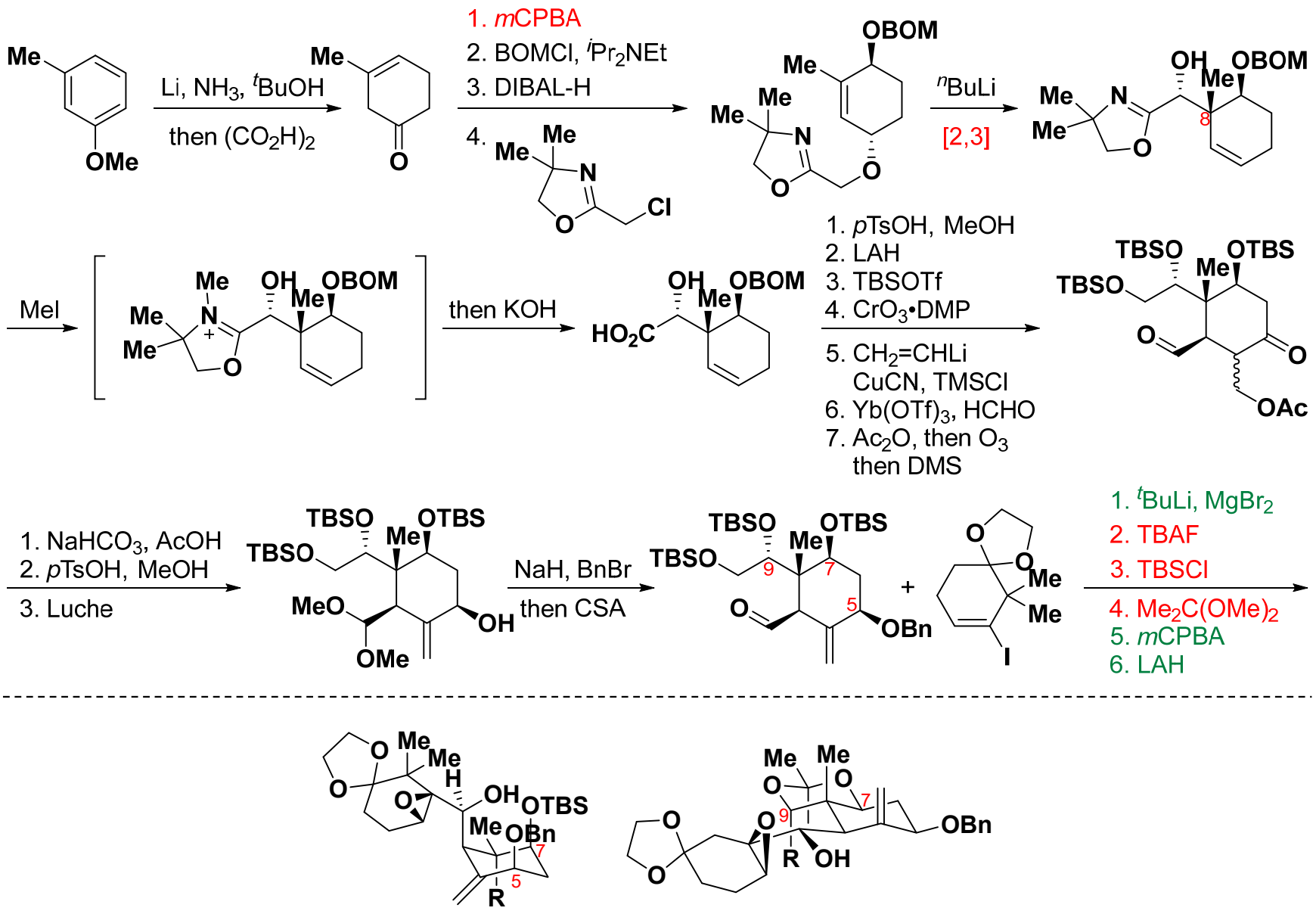




- C1-C2 bond formation via NHK?
- Introduction of C12 methyl group before construction of B ring

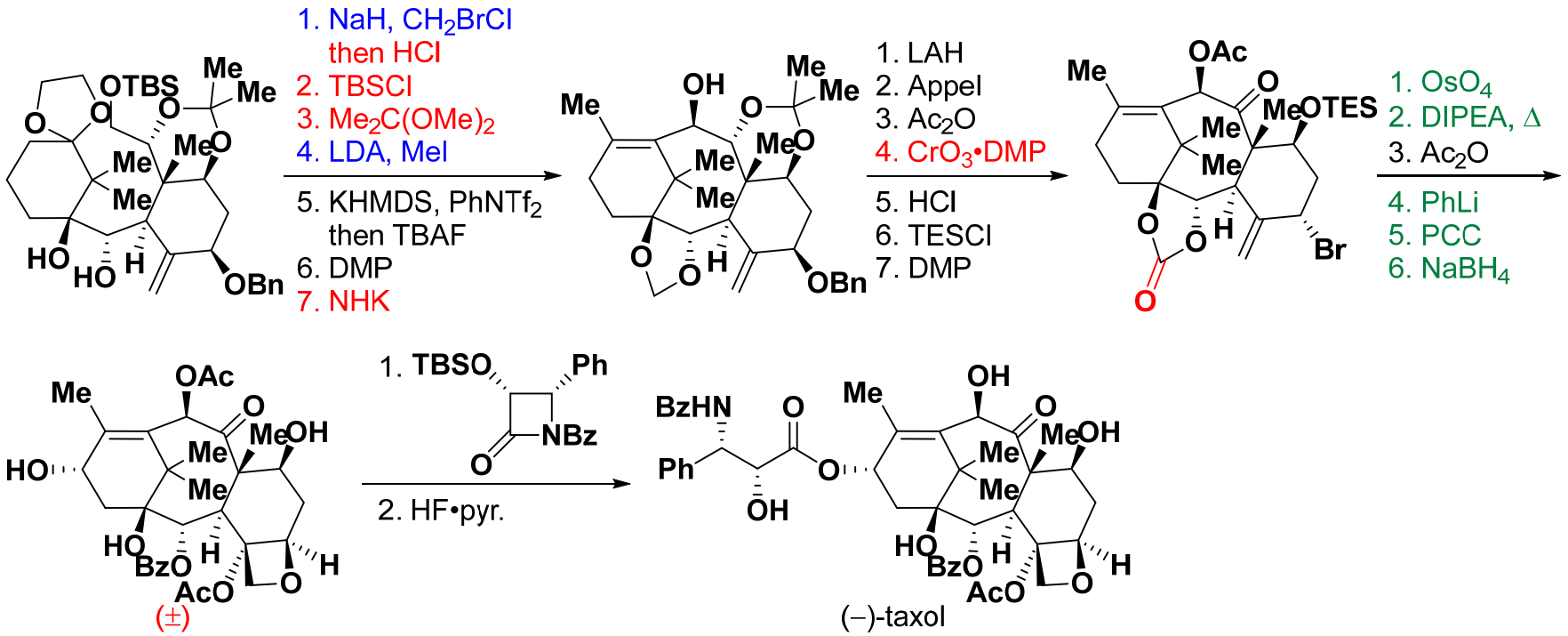
Sheng, X. C. A. Total Synthesis of (+)-O-Cinnamoyltaxicin-I Triacetate Ph.D. Thesis, Harvard University, 1998.

Kishi's work



Lim, J. A. A Total Synthesis of Taxol. Ph.D. Thesis, Harvard University, 2000.

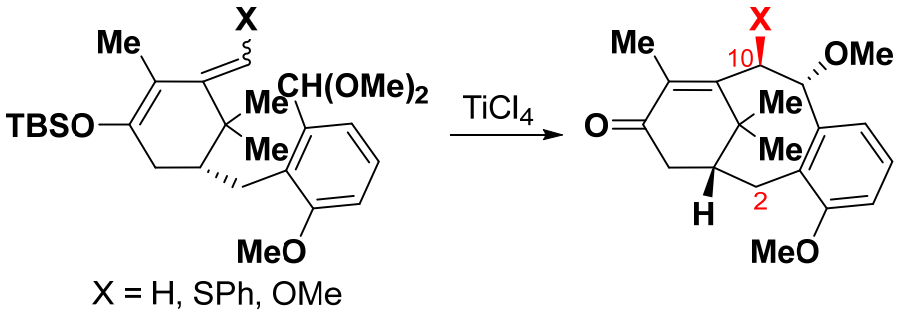
Kishi's work



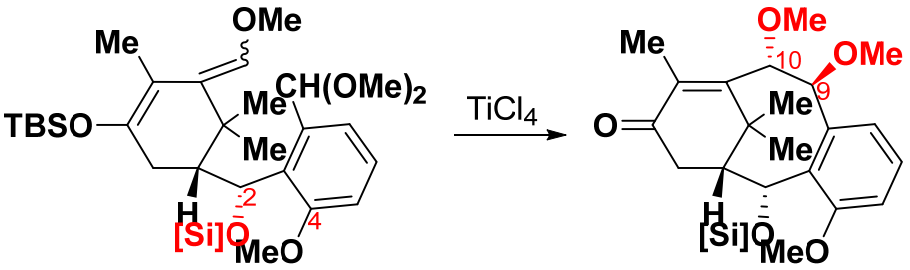
- Convergent
- Conformation control
- Construction of C8 quaternary carbon centre via [2,3]
- C10-C11 bond formation via NHK
- ……

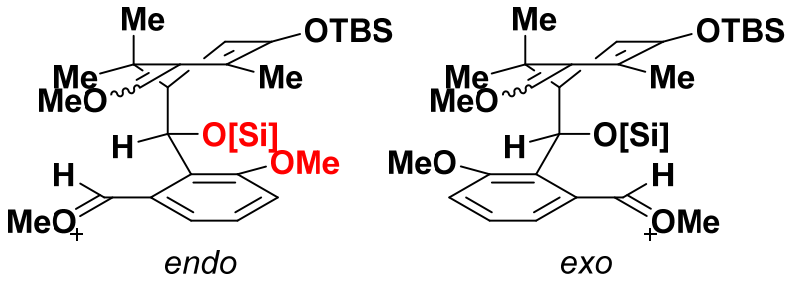
Lim, J. A. A Total Synthesis of Taxol. Ph.D. Thesis, Harvard University, 2000.

Kuwajima's work



X = H, SPh, OMe

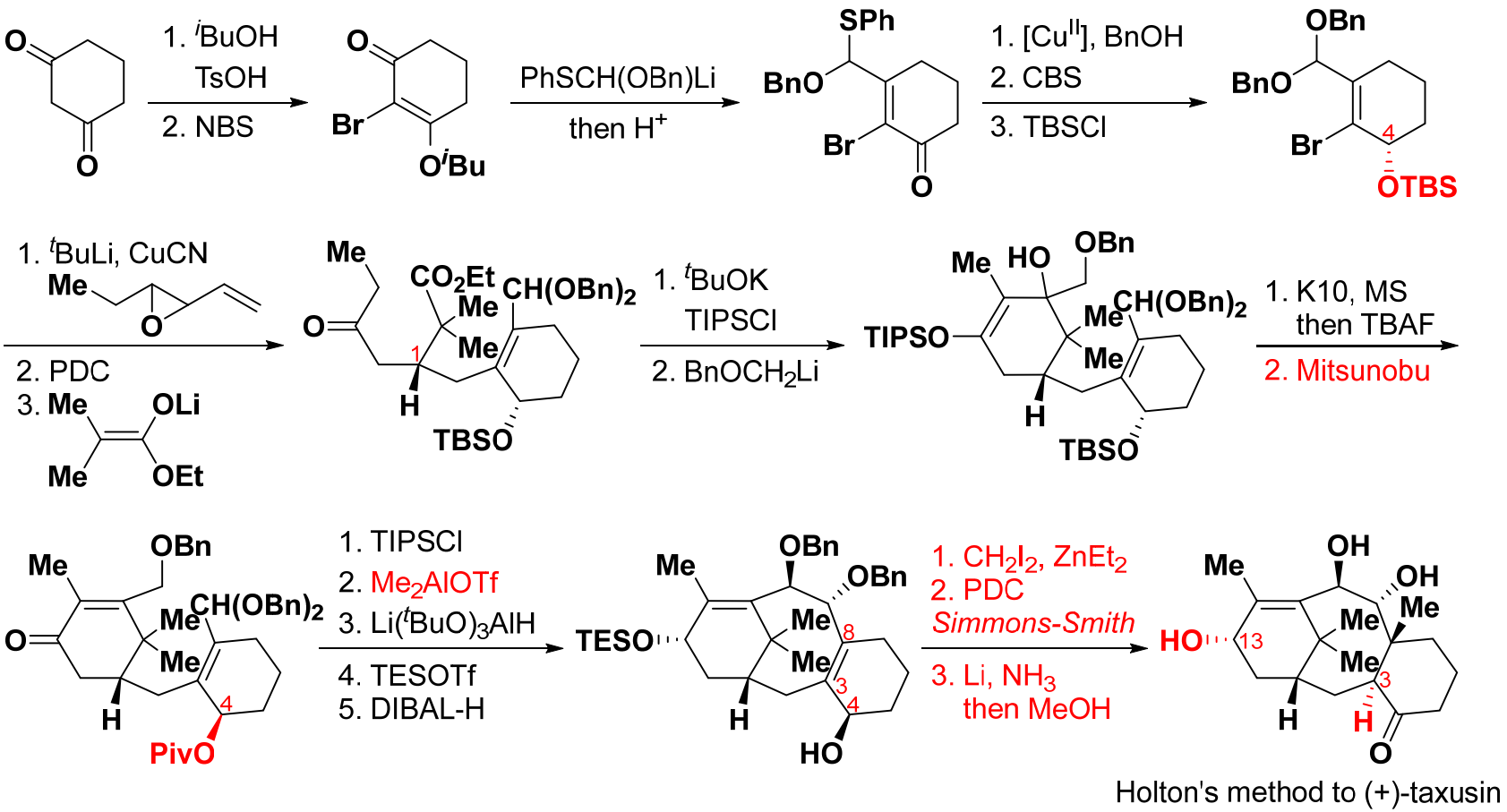




- For taxusin, √
- For taxol, in situ chelation of C2 C4 oxygen atoms

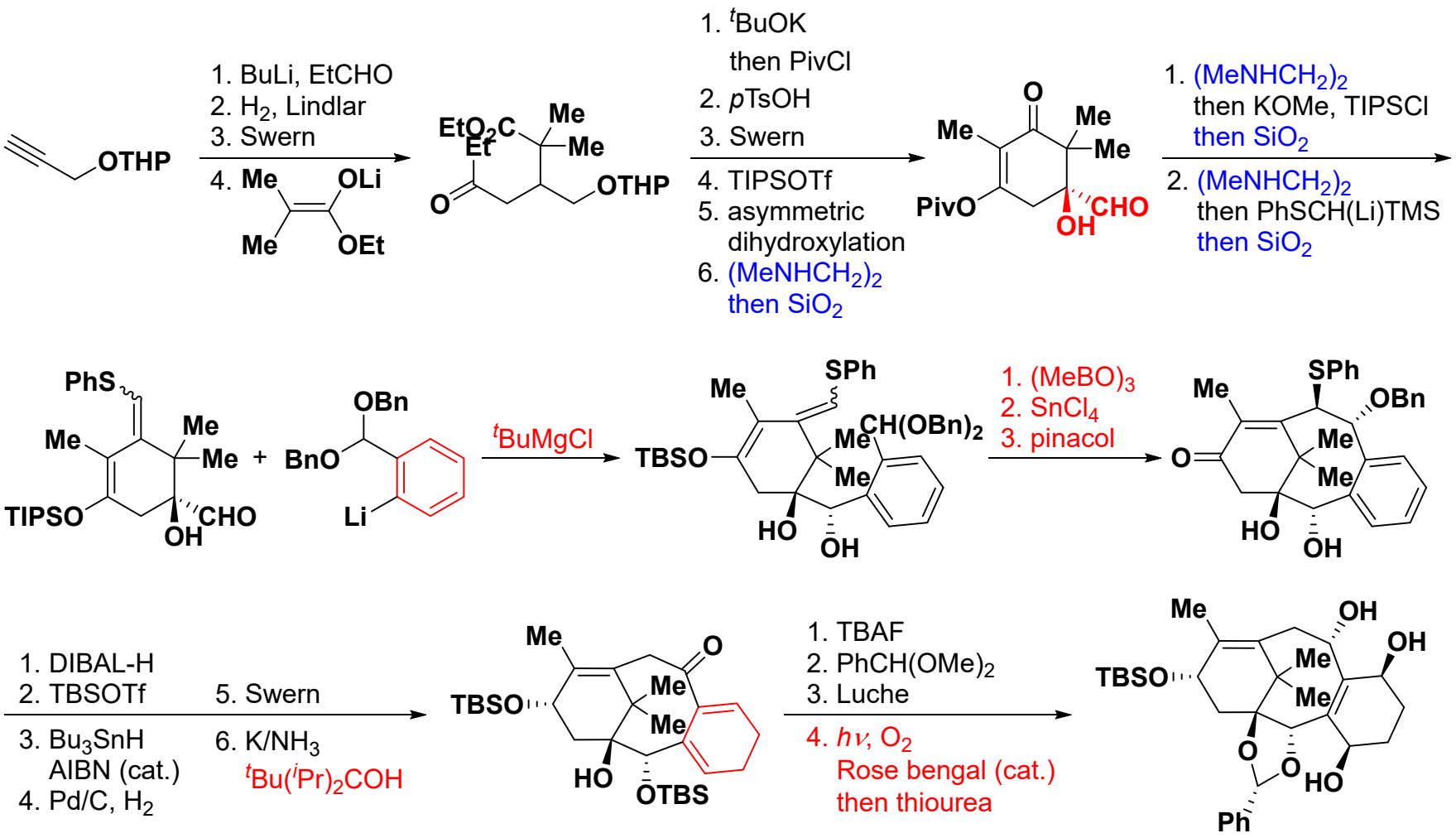
Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 8277.
Seto, M.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *J. Org. Chem.* **1994**, *59*, 3165.

Kuwajima's work



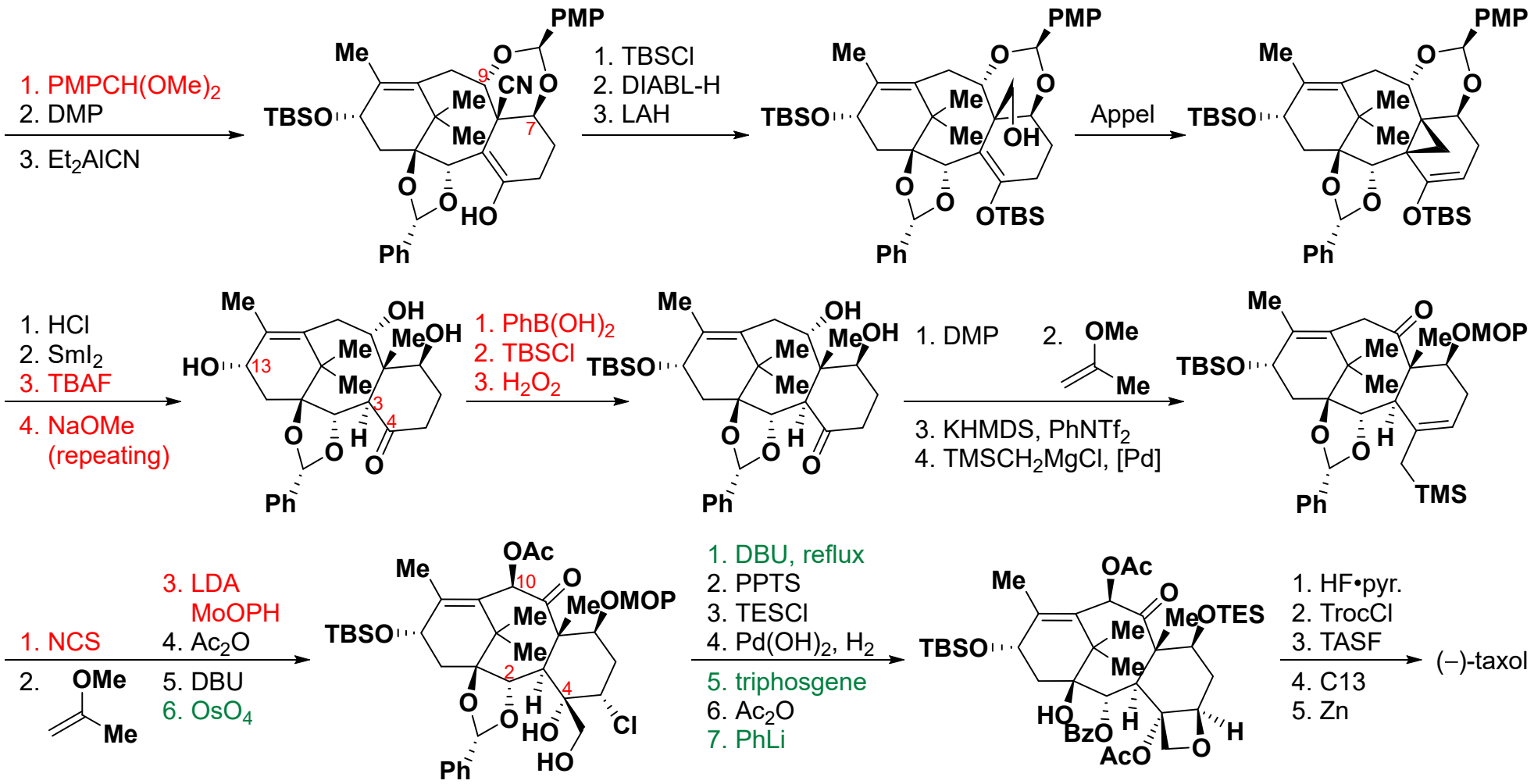
Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1999**, *121*, 3072.

Kuwajima's work



Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811.

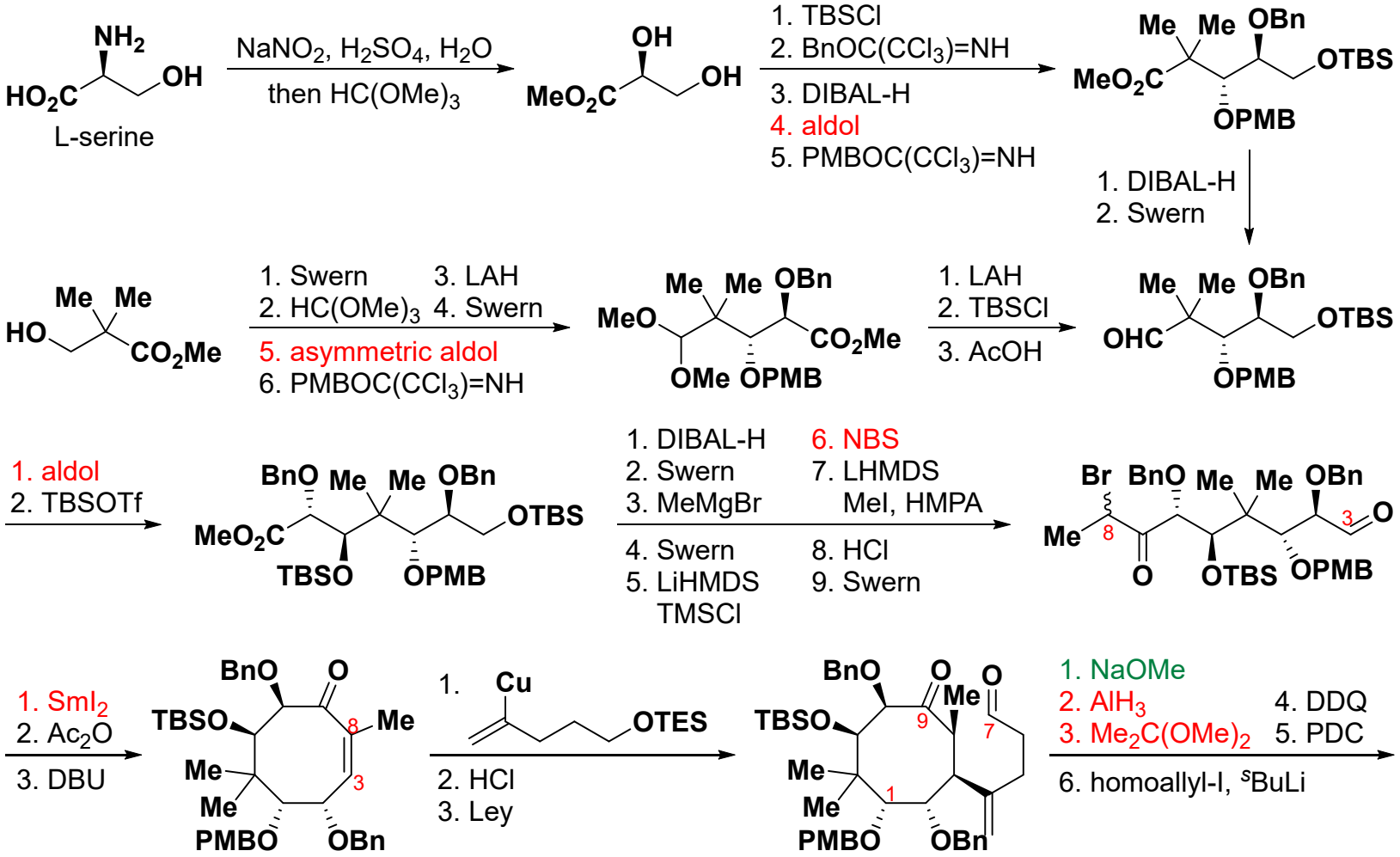
Kuwajima's work



- Control of atropisomerism
- C2-C3, C9-C10 bonds formation
- C7 C9 oxidation
- Introduction of C19 methyl group

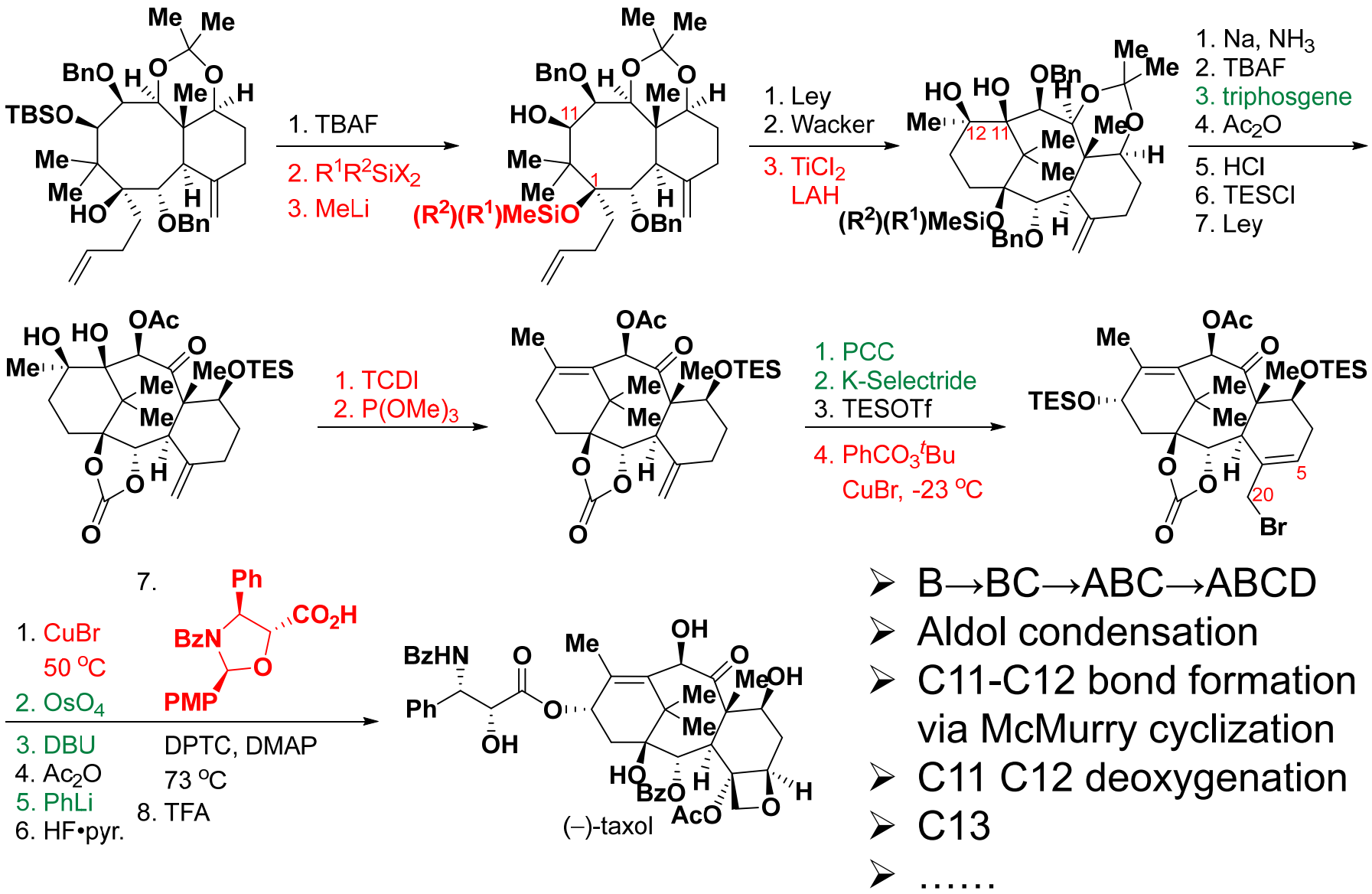
Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811.

Mukaiyama's work



Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121.

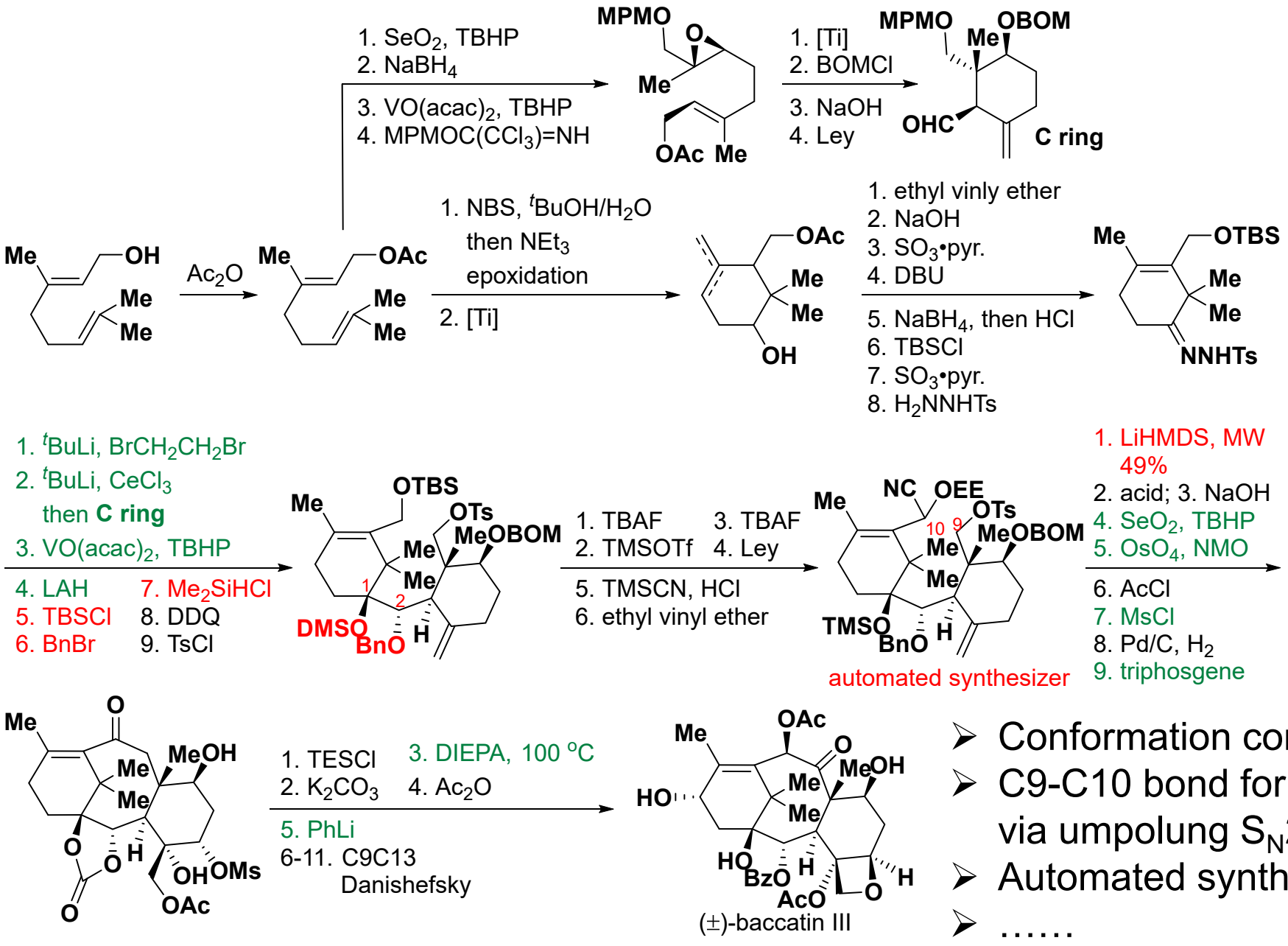
Mukaiyama's work



- B→BC→ABC→ABCD
- Aldol condensation
- C11-C12 bond formation via McMurry cyclization
- C11 C12 deoxygenation
- C13
- ……

Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121.

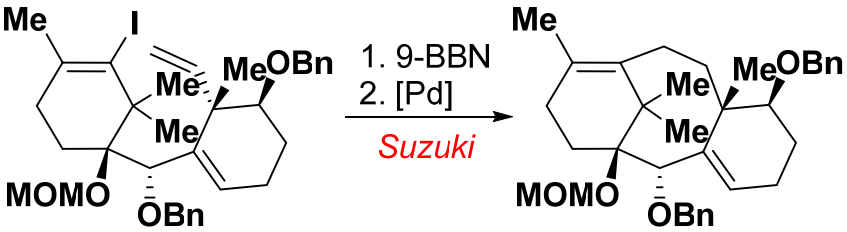
Takahashi's work

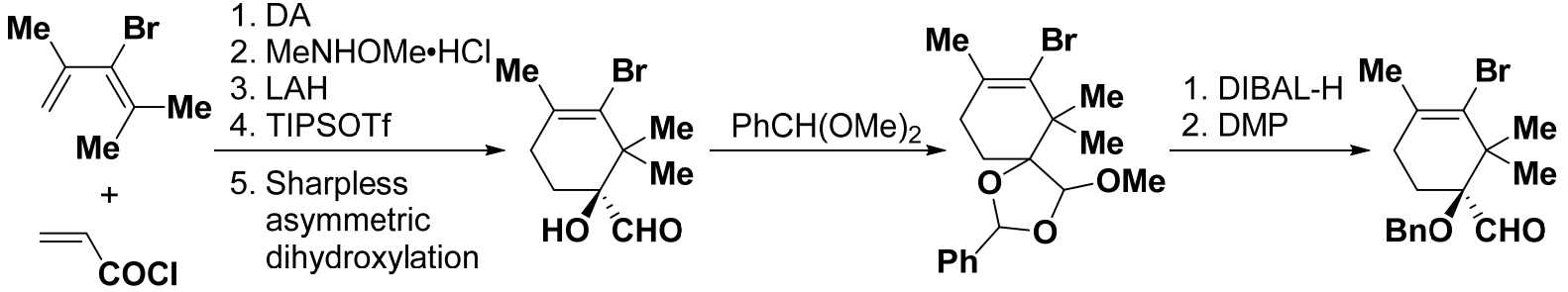


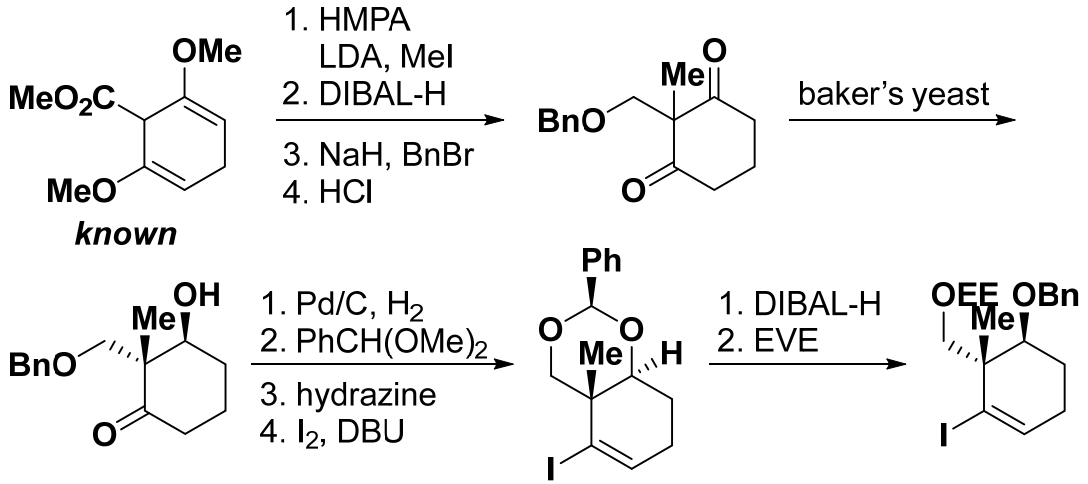
- Conformation control
- C9-C10 bond formation via umpolung S_N2
- Automated synthesizer
- ……

Doi, T.; Fuse, S.; Miyamoto, S.; Nakai, K.; Sasuga, D.; Takahashi, T. *Chem. Asian J.* **2006**, *1*, 370.

Nakada's work

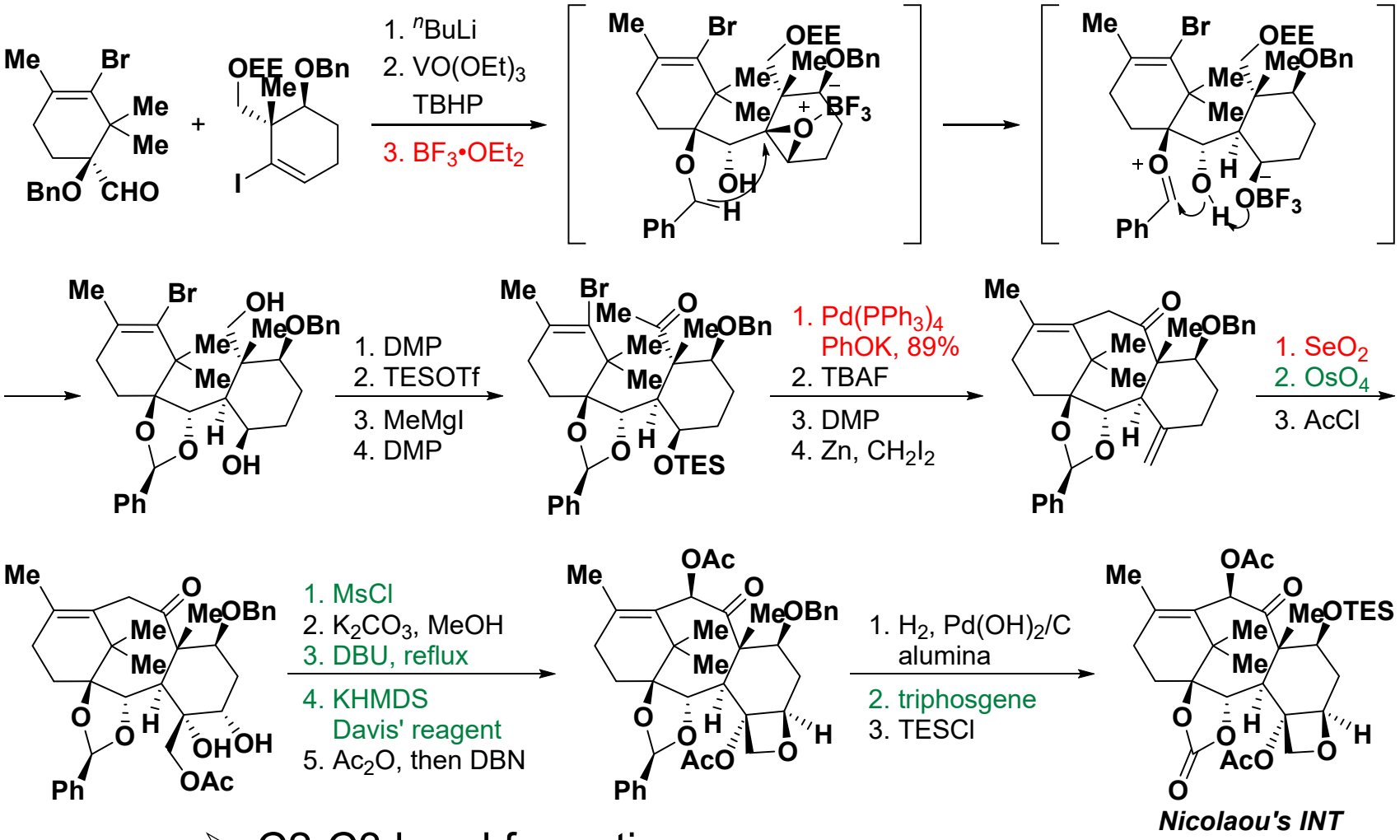






Kawada, H.; Iwamoto, M.; Utsugi, M.; Miyano, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 4491.
Hirai, S.; Utsugi, M.; Iwamoto, M.; Nakada, M. *Chem. Eur. J.* **2015**, *21*, 355.

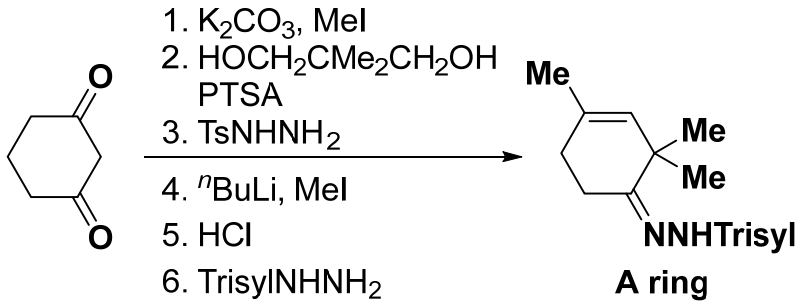
Nakada's work

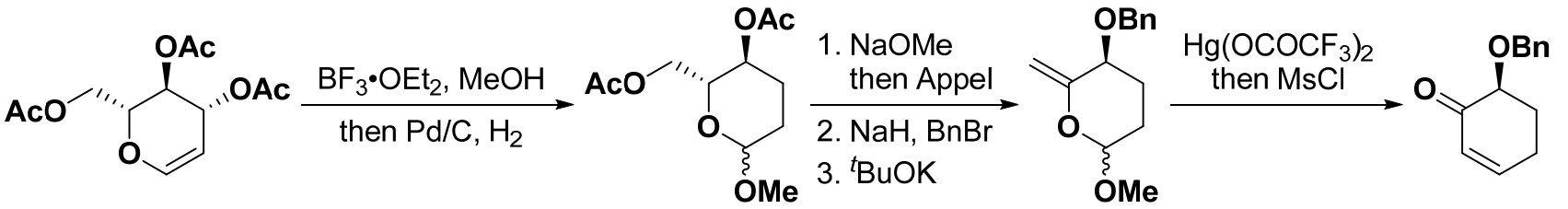


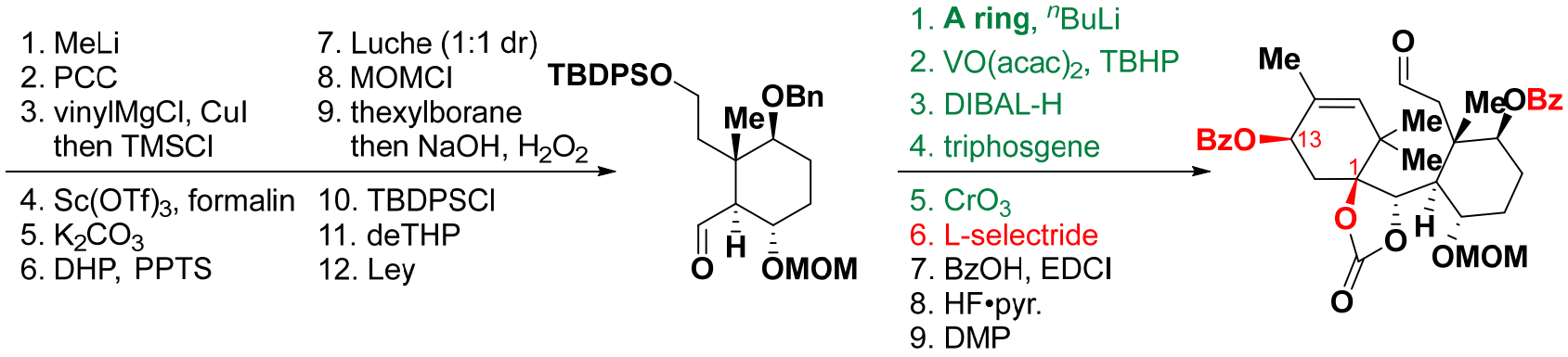
- C2-C3 bond formation
- 1,5-hydride shift–benzylidene formation
- C10-C11 bond formation via palladium chemistry

Hirai, S.; Utsugi, M.; Iwamoto, M.; Nakada, M. *Chem. Eur. J.* **2015**, *21*, 355.

Chida's work

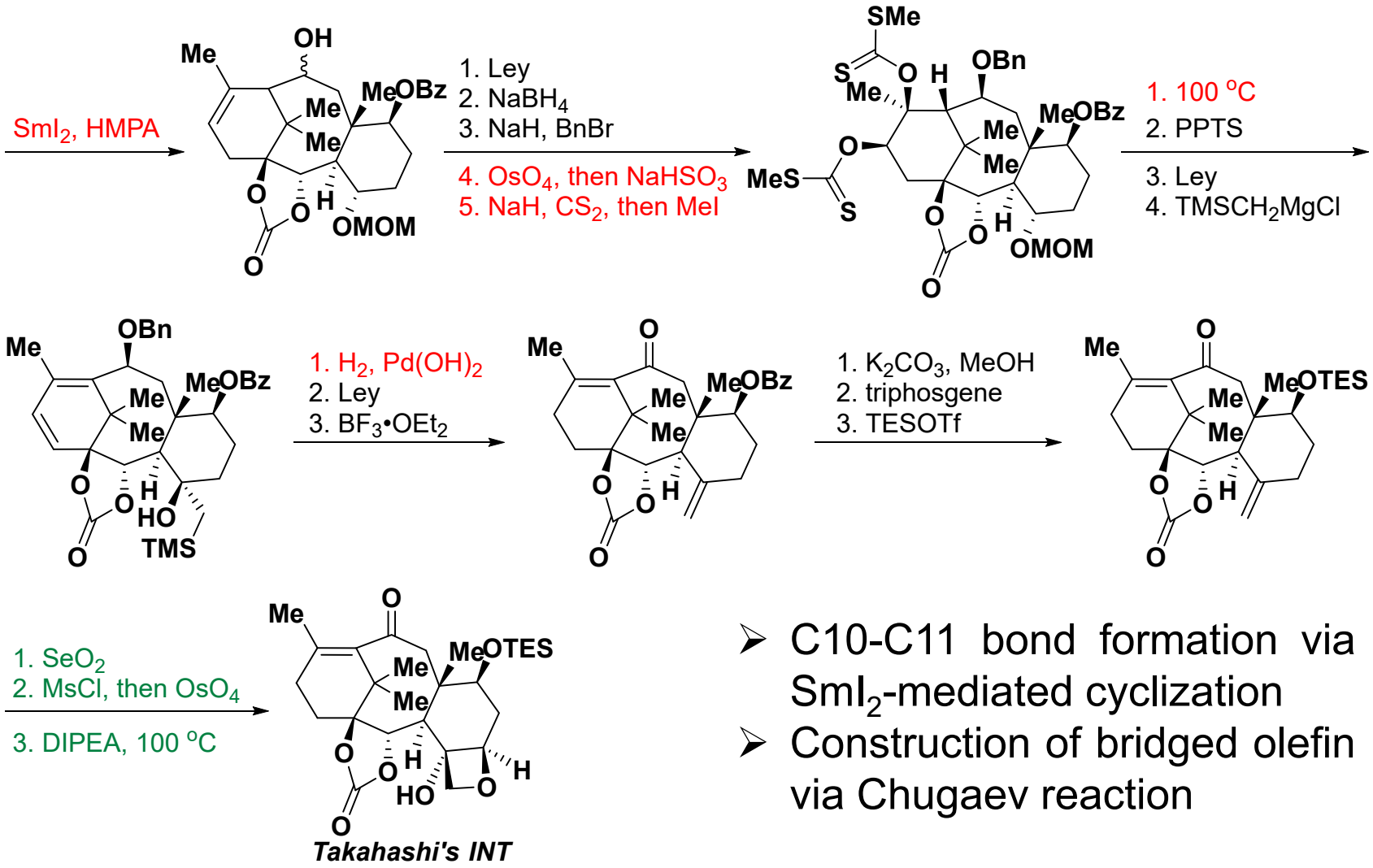






Fukaya, K.; Tanaka, Y.; Sato, A. C.; Kodama, K.; Yamazaki, H.; Ishimoto, T.; Nozaki, Y.; Iwaki, Y. M.; Yuki, Y.; Umei, K.; Sugai, T.; Yamaguchi, Y.; Watanabe, A.; Oishi, T.; Sato, T.; Chida, N. *Org. Lett.* **2015**, *17*, 2570.

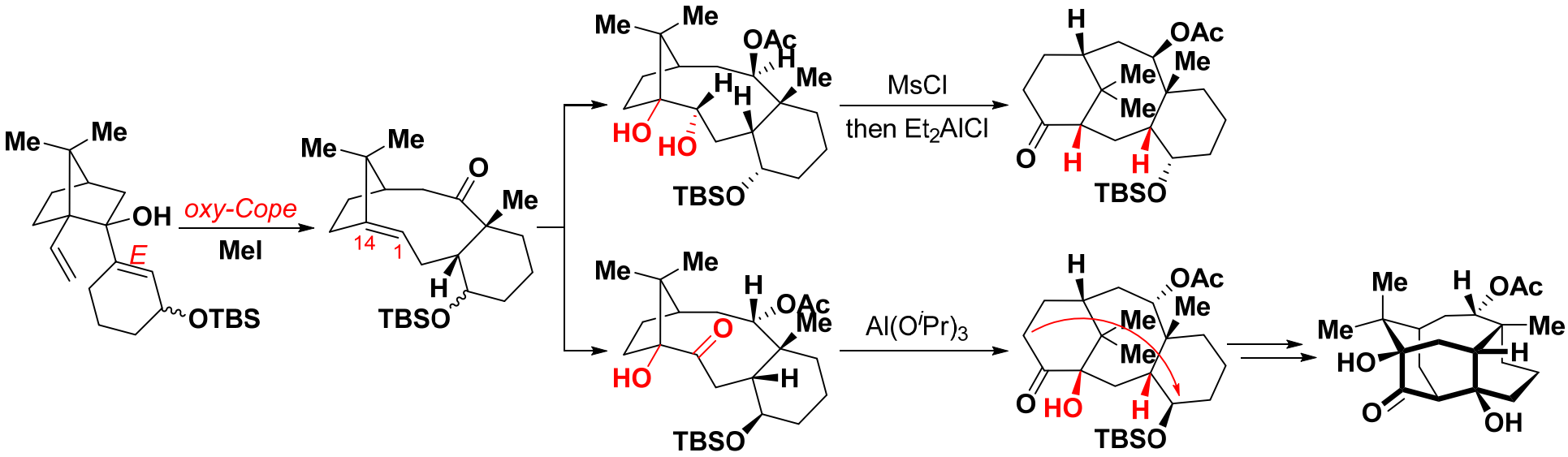
Chida's work



- C10-C11 bond formation via SmI_2-mediated cyclization
- Construction of bridged olefin via Chugaev reaction

Fukaya, K.; Tanaka, Y.; Sato, A. C.; Kodama, K.; Yamazaki, H.; Ishimoto, T.; Nozaki, Y.; Iwaki, Y. M.; Yuki, Y.; Umei, K.; Sugai, T.; Yamaguchi, Y.; Watanabe, A.; Oishi, T.; Sato, T.; Chida, N. *Org. Lett.* **2015**, *17*, 2570. *Org. Lett.* **2015**, *17*, 2574.

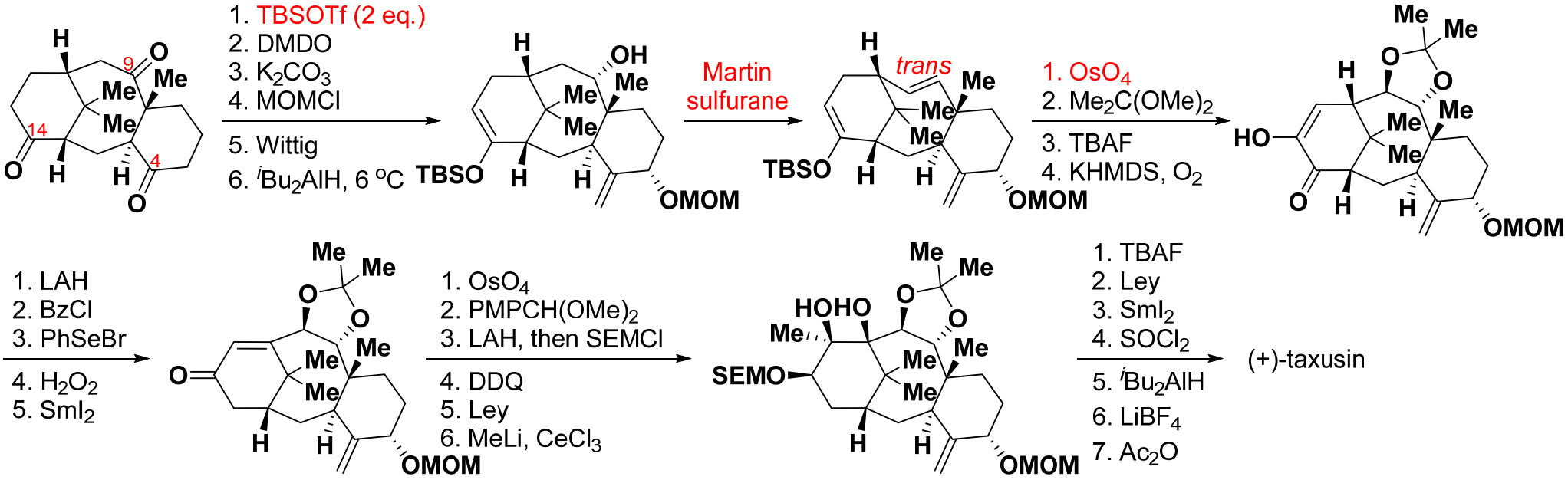
Paquette's work



C4 oxidation before rearrangement

Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203.
Paquette, L. A.; Wang, H.-L.; Su, Z.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5213.

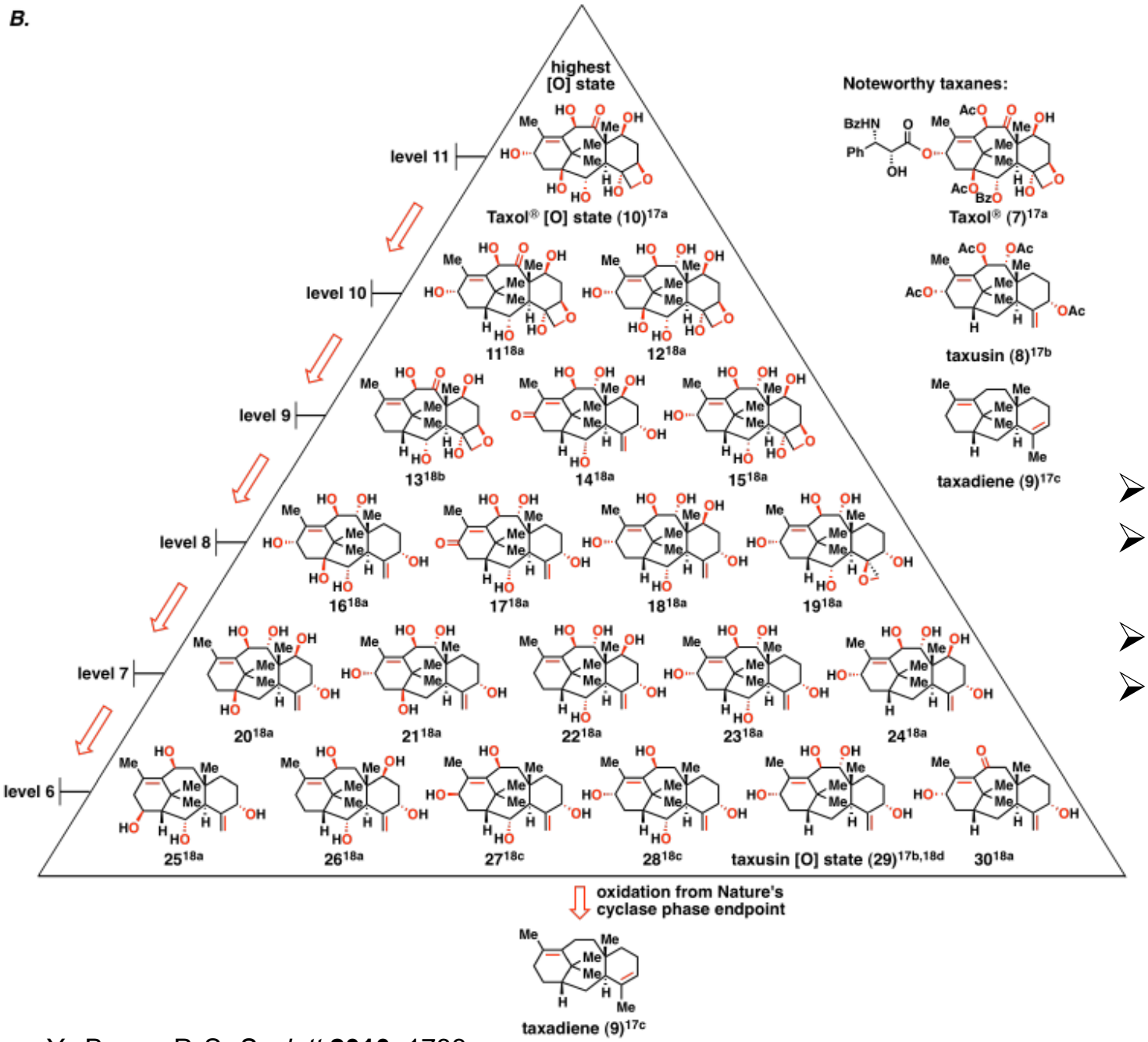
Paquette's work



- [3,3] & semi-pinacol rearrangement
- C9 C10 oxidation via dihydroxylation of trans olefin

Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203.
Paquette, L. A.; Wang, H.-L.; Su, Z.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5213.

Baran's work: two-phase synthesis

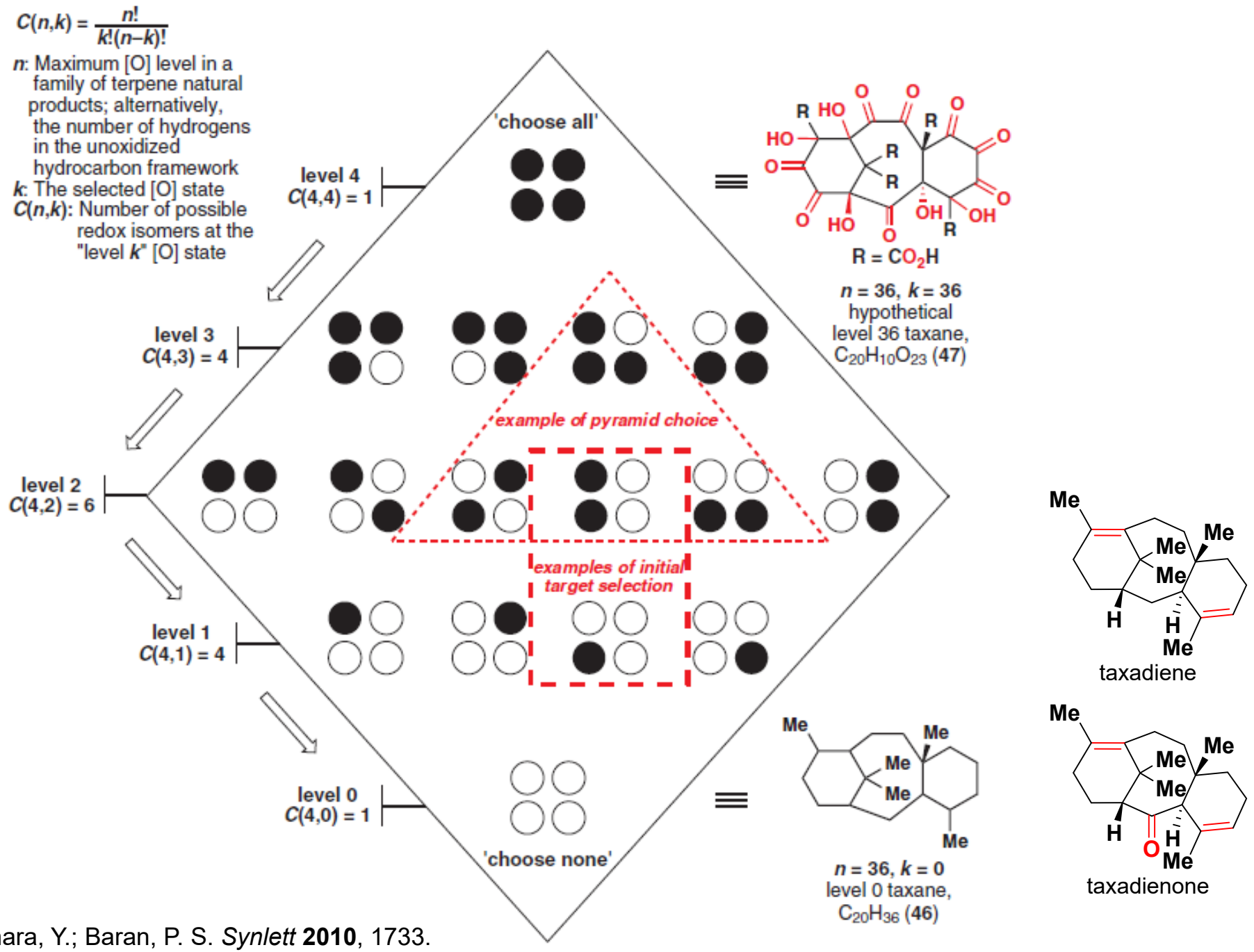


- Divergent synthesis
- SAR

- Linear synthesis
- Differentiations of functional groups at late stage

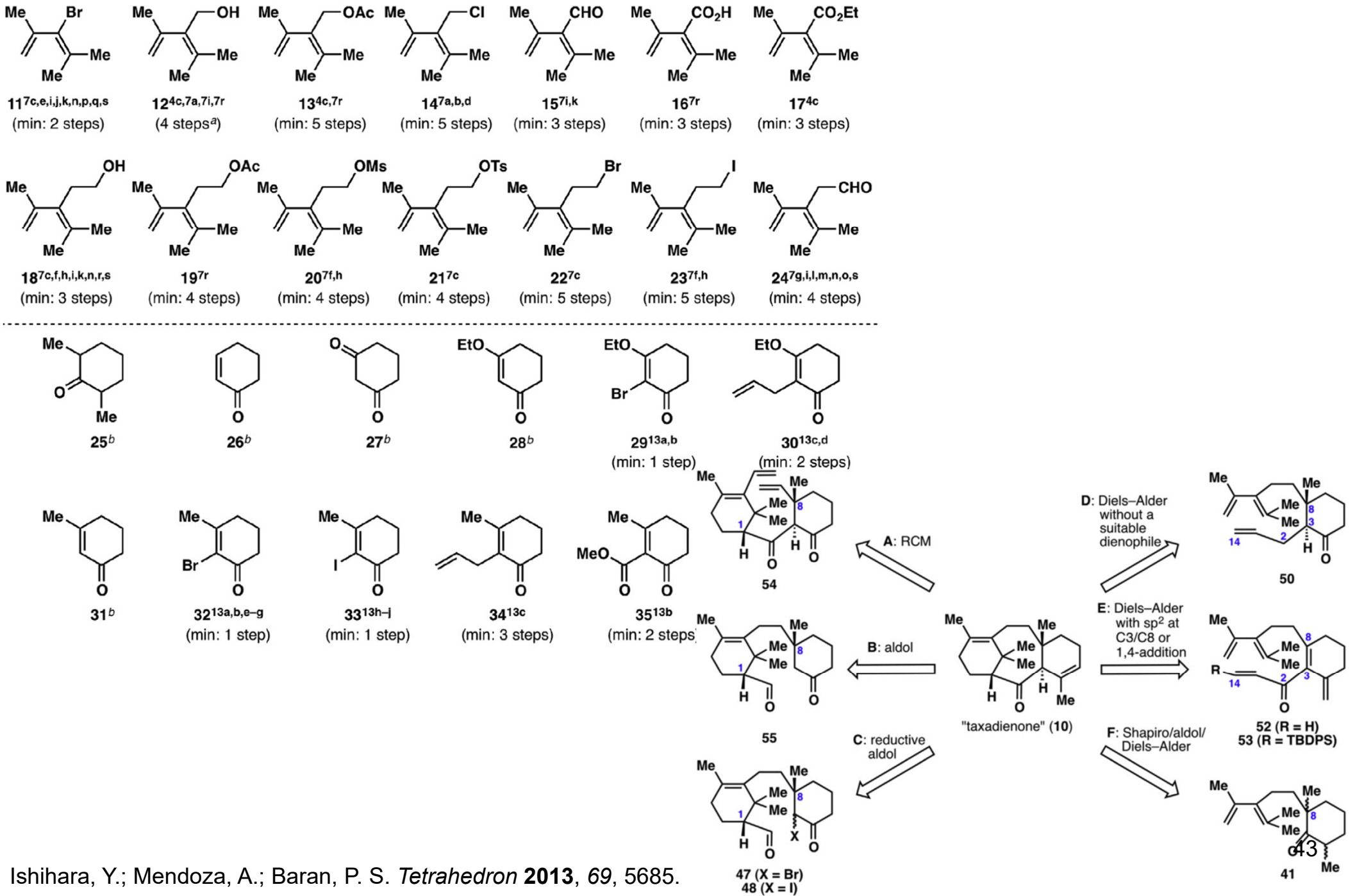
Ishihara, Y.; Baran, P. S. *Synlett* **2010**, 1733.

Baran's work: two-phase synthesis



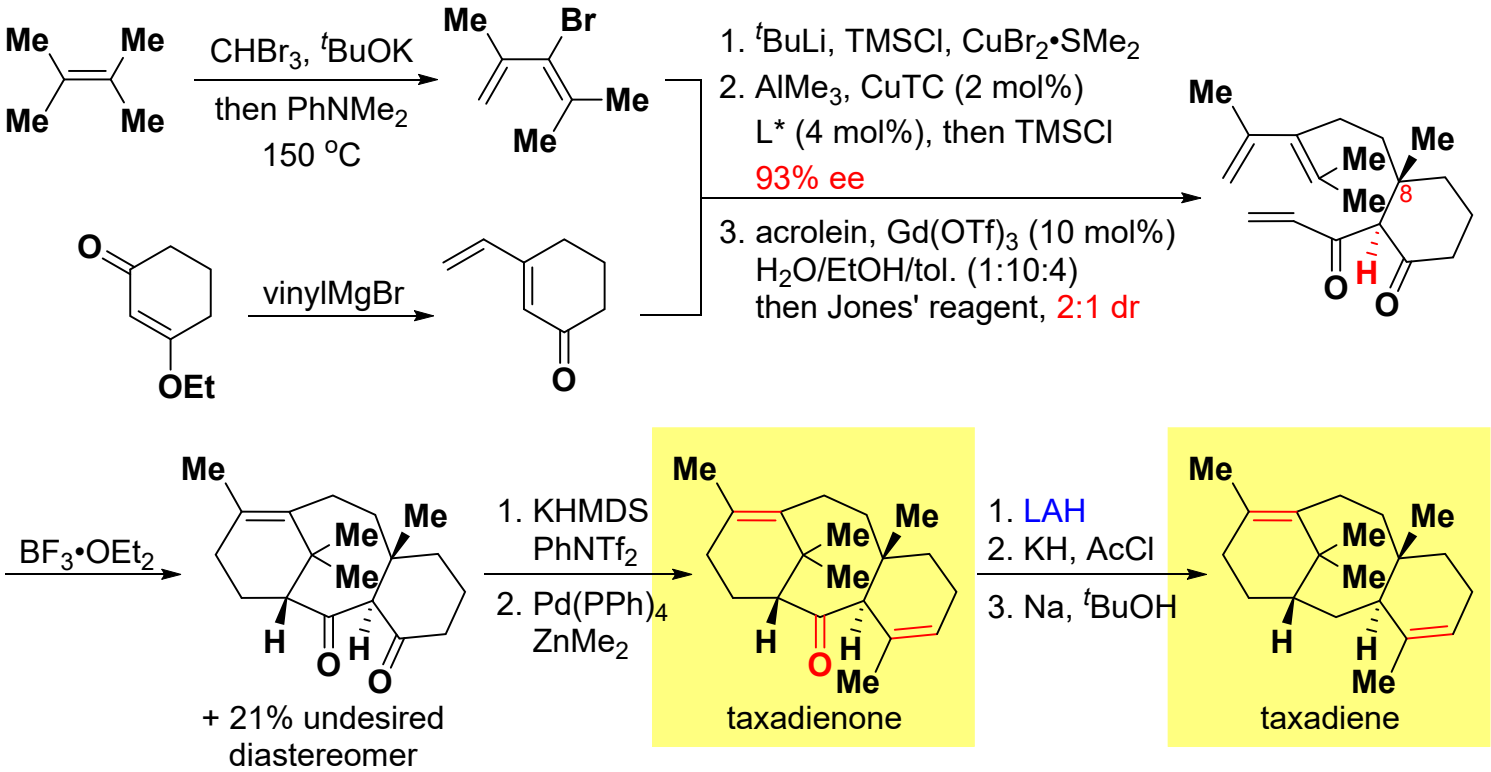
Ishihara, Y.; Baran, P. S. *Synlett* **2010**, 1733.

Baran's work: two-phase synthesis



Ishihara, Y.; Mendoza, A.; Baran, P. S. *Tetrahedron* **2013**, *69*, 5685.

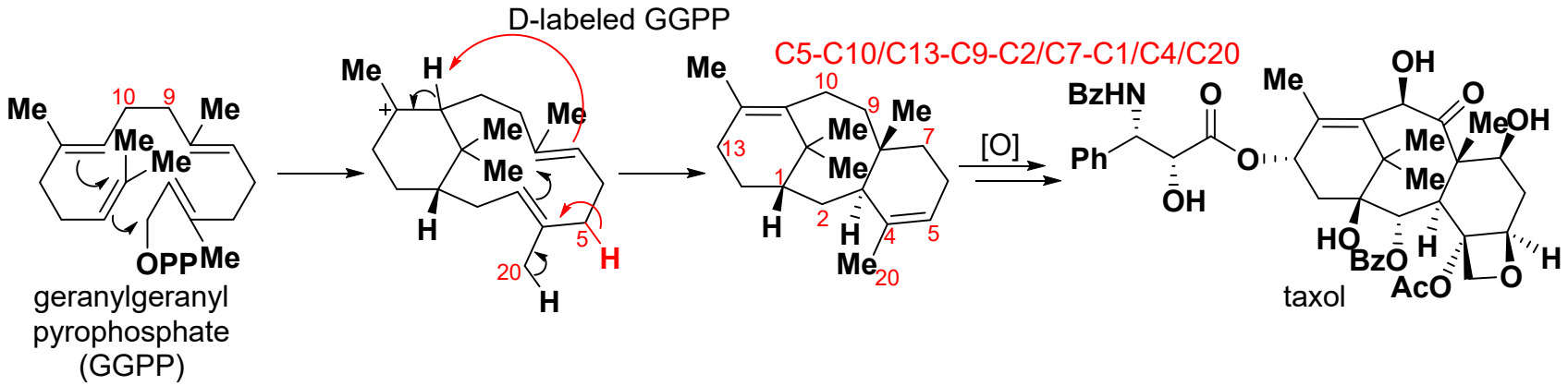
Baran's work: two-phase synthesis

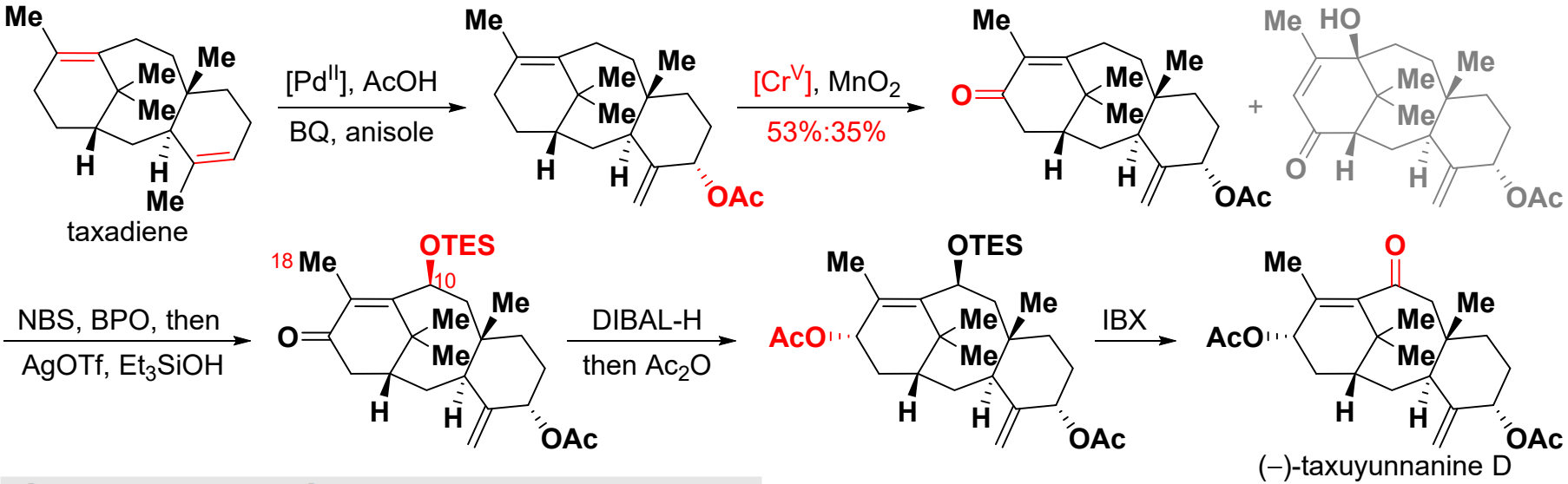


- C8 quaternary carbon centre
- Short, convergent and scalable

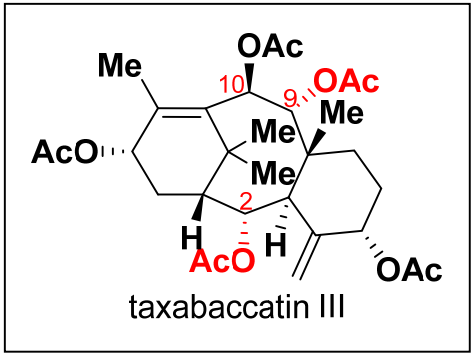
Mendoza, A.;Ishihara, Y.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 21.

Baran's work: two-phase synthesis





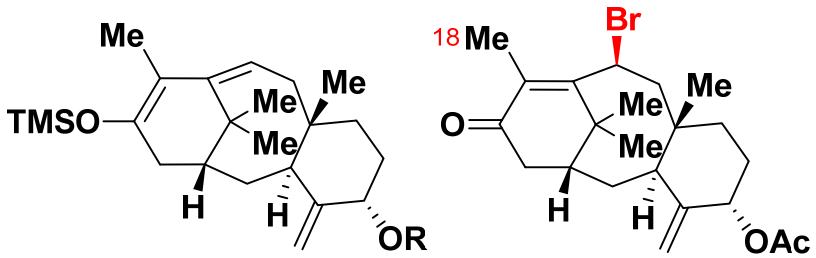
[allylic C–H oxidation panel]		substrate		
category	conditions	1 [C-5]	4 [C-13]	5[a] [C-10]
1	$Pd(OAc)_2$, BQ	yes	no	no
2	Cr^{V} or Cr^{VI}	no	yes	no
3	NBS, $(BzO)_2$	no	no	yes
4	M cat., ROOR′	no	no	no
5	SeO_2 or $^1O_2$	no[b]	no[c]	no



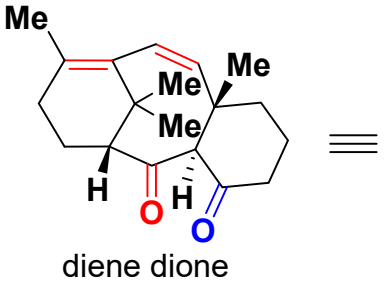
Wilde, N. C.; Isomura, M.; Mendoza, A.;Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4909.

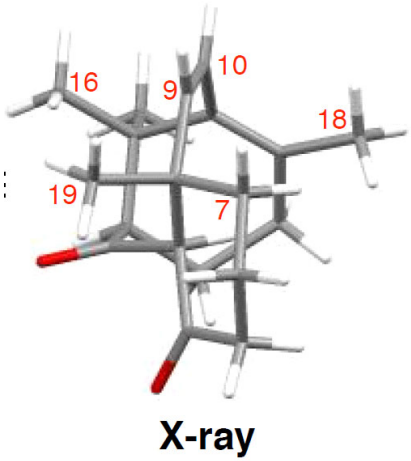
Baran's work: two-phase synthesis

- Oxidase phase

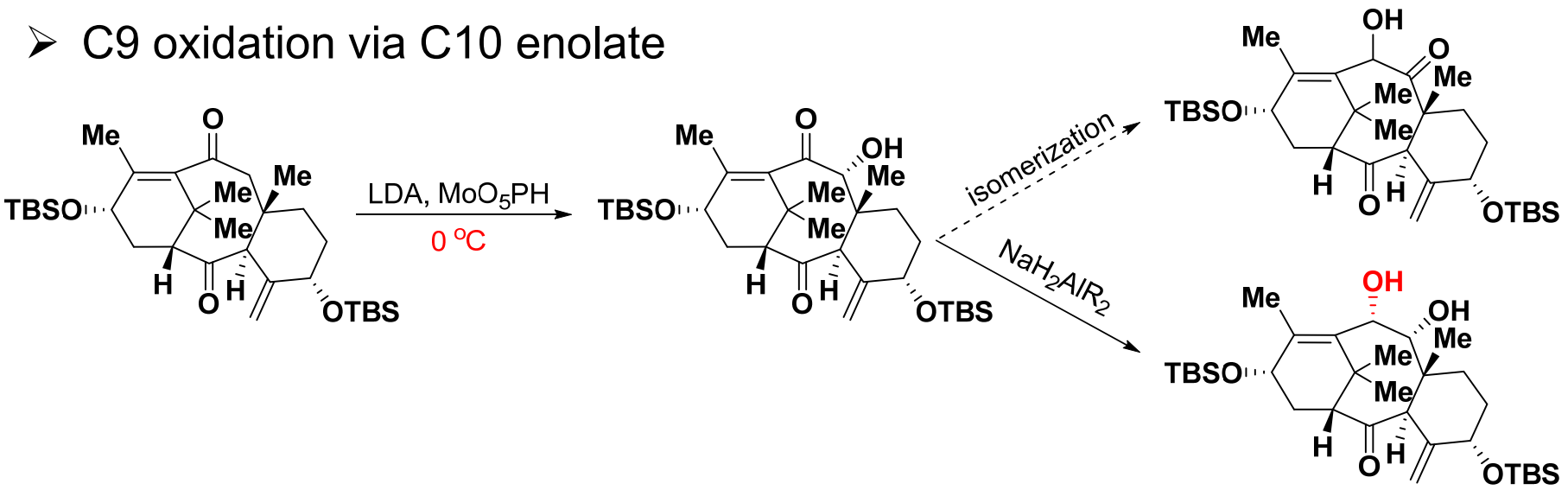


- Cyclase phase





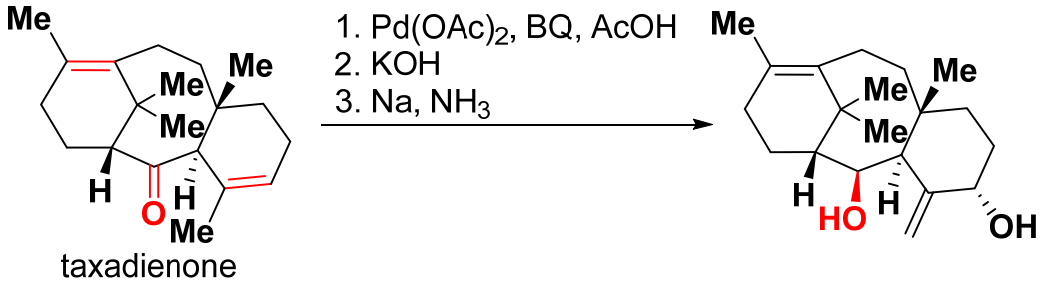
- C9 oxidation via C10 enolate



Wilde, N. C. The Two-Phase Synthesis of Taxane Natural Products: Developing the Tools for the Oxidase Phase, Ph.D. Thesis, The Scripps Research Institute, 2016.

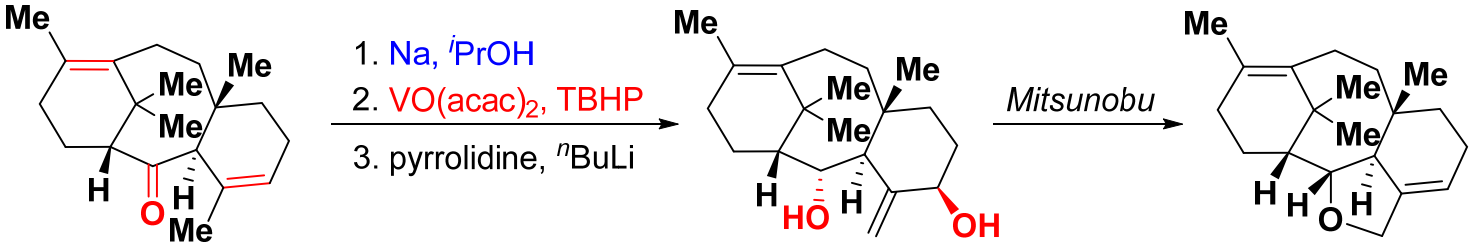
Baran's work: two-phase synthesis

- C5-C2



taxadienone

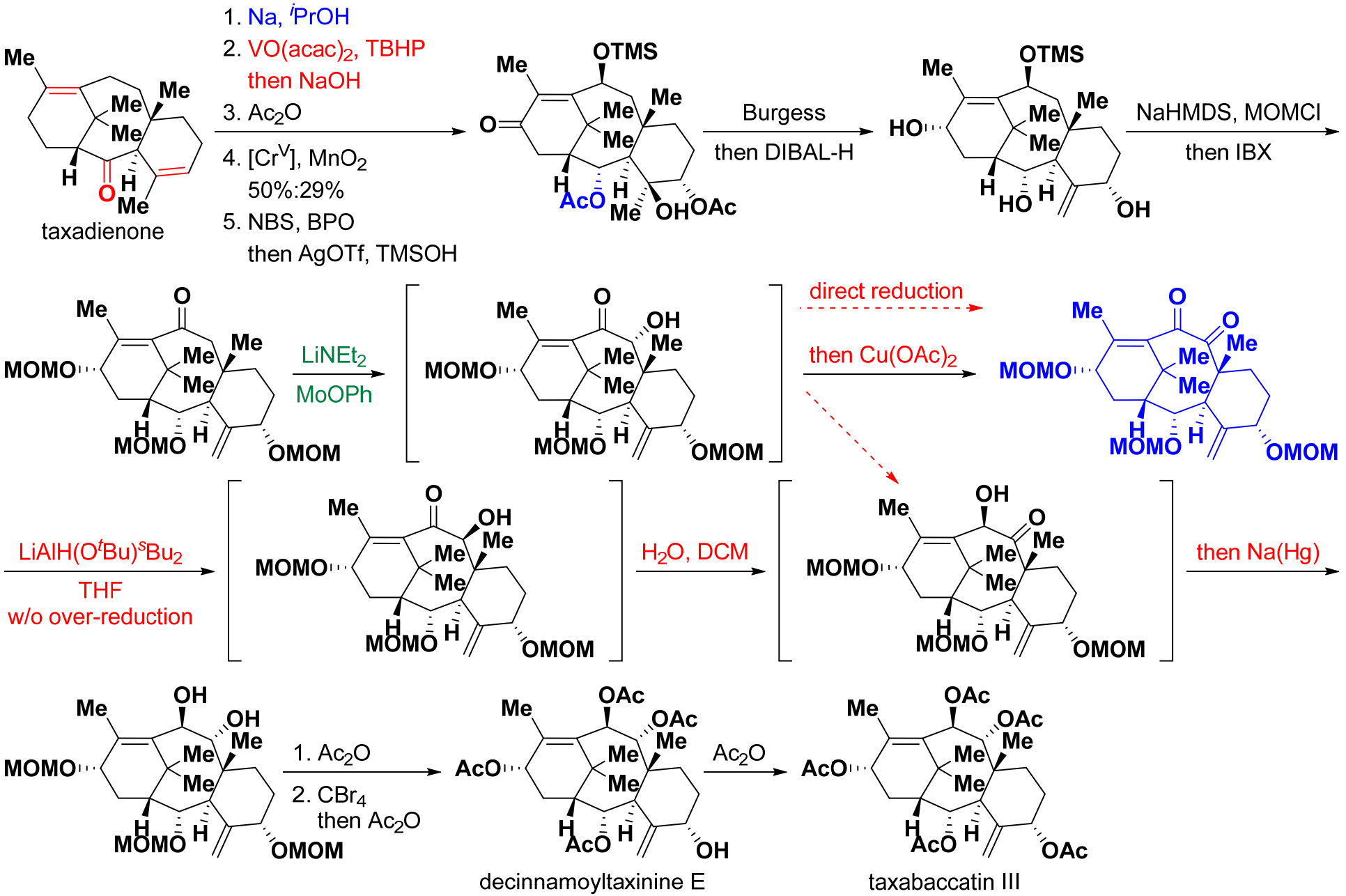
- C2-C5



taxadienone

Wilde, N. C. The Two-Phase Synthesis of Taxane Natural Products: Developing the Tools for the Oxidase Phase, Ph.D. Thesis, The Scripps Research Institute, 2016.

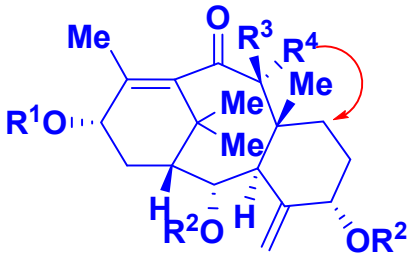
Baran's work: two-phase synthesis



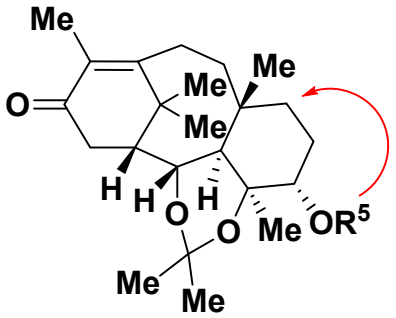
Yuan, C.; Jin, Y.; Wilde, N. C.; Baran, P. S. *Angew. Chem. Int. Ed.* **2016**, *55*, 8280.

Baran's work: two-phase synthesis

- C7 oxidation

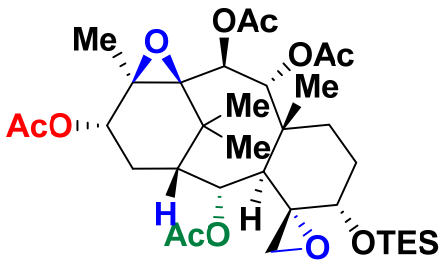


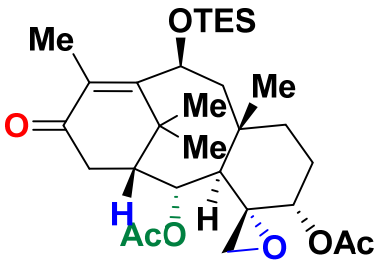
$R^3 = R^4$ = NR, CHOH
R^3 = H, R^4 = $OC(O)R$, $OS(O)_2R$
$OSiEt_2R$, OR,
CMe_2OH

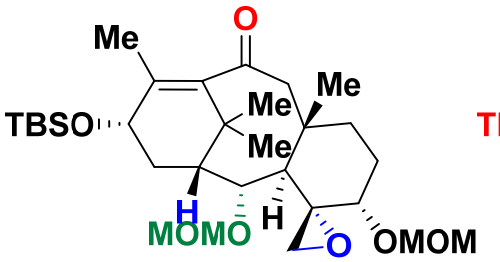


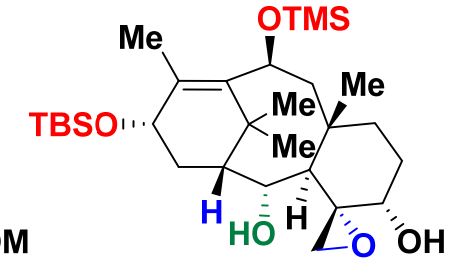
R^5 = $OC(O)R$, $OS(O)_2NH_2$, OR

- C1 oxidation: DMDO

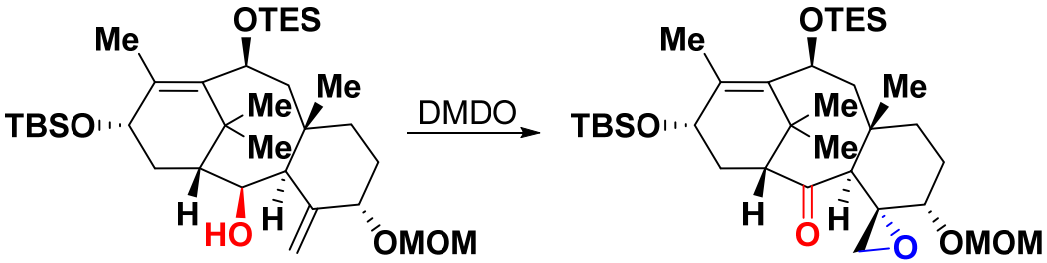








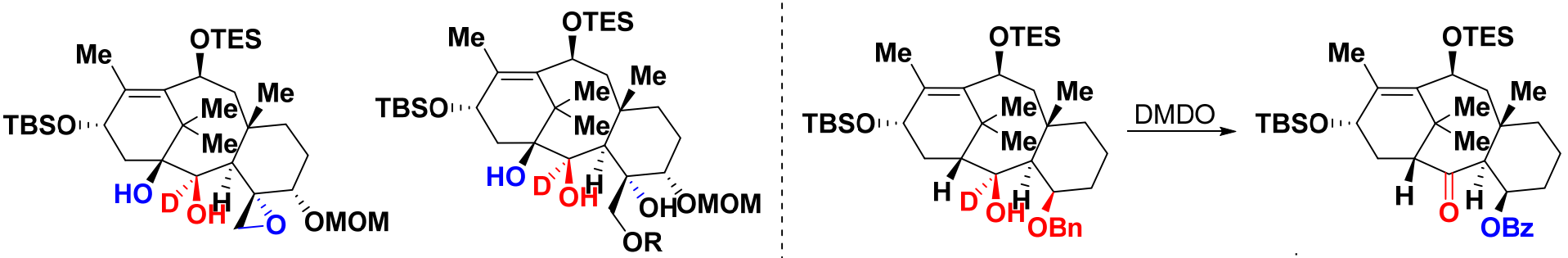
- C2-β-OH



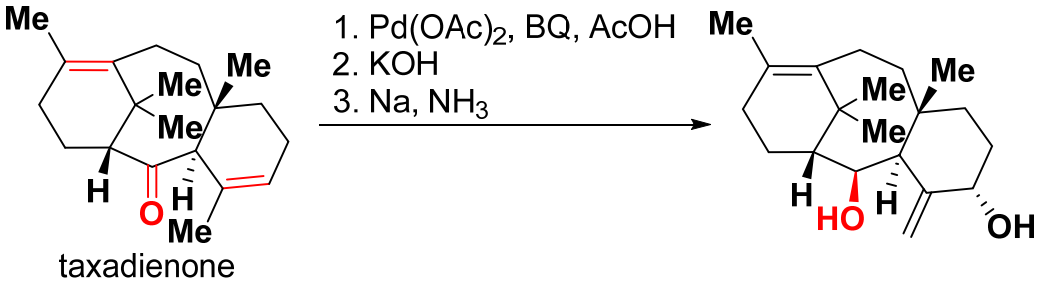
Kanda, Y.; Nakamura, H.; Umemiya, S.; Puthukanoori, R. K.; Appala, V. R. M.; Gaddamanugu, G. K.; Paraselli, B. R.; Baran, P. S. *J. Am. Chem. Soc.* **2020** *142*, 10526. Kanda, Y;. Ishihara, Y.; Wilde, N. C.; Baran, P. S. *J. Org. Chem.* **2020**, *85*, 10293.

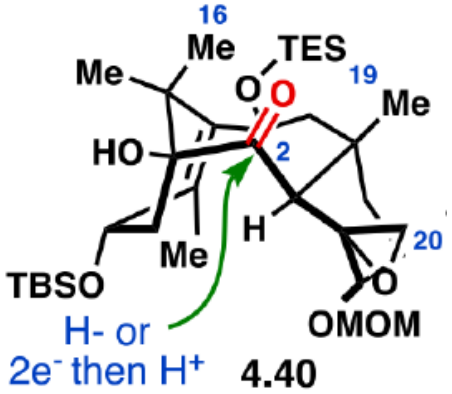
Baran's work: two-phase synthesis

- KIE assisted chemoselective oxidation



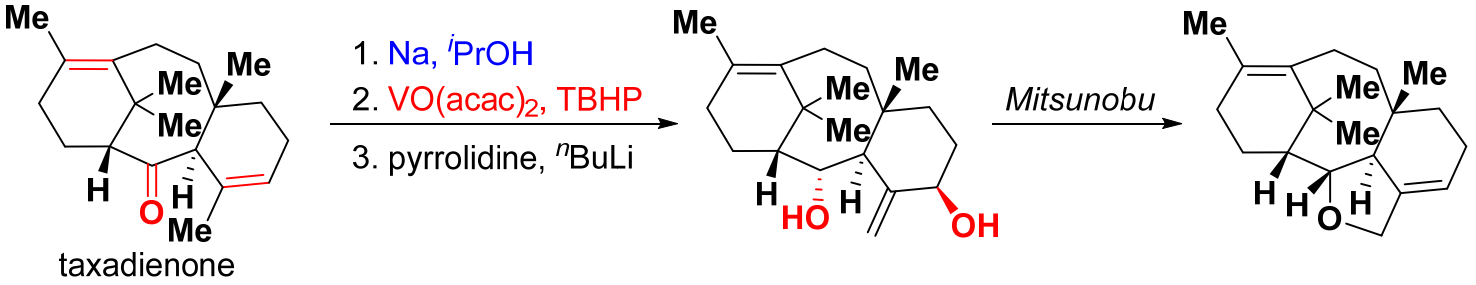
- C5-C2

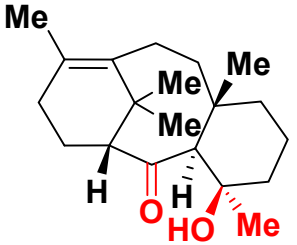




C4 is important!!!

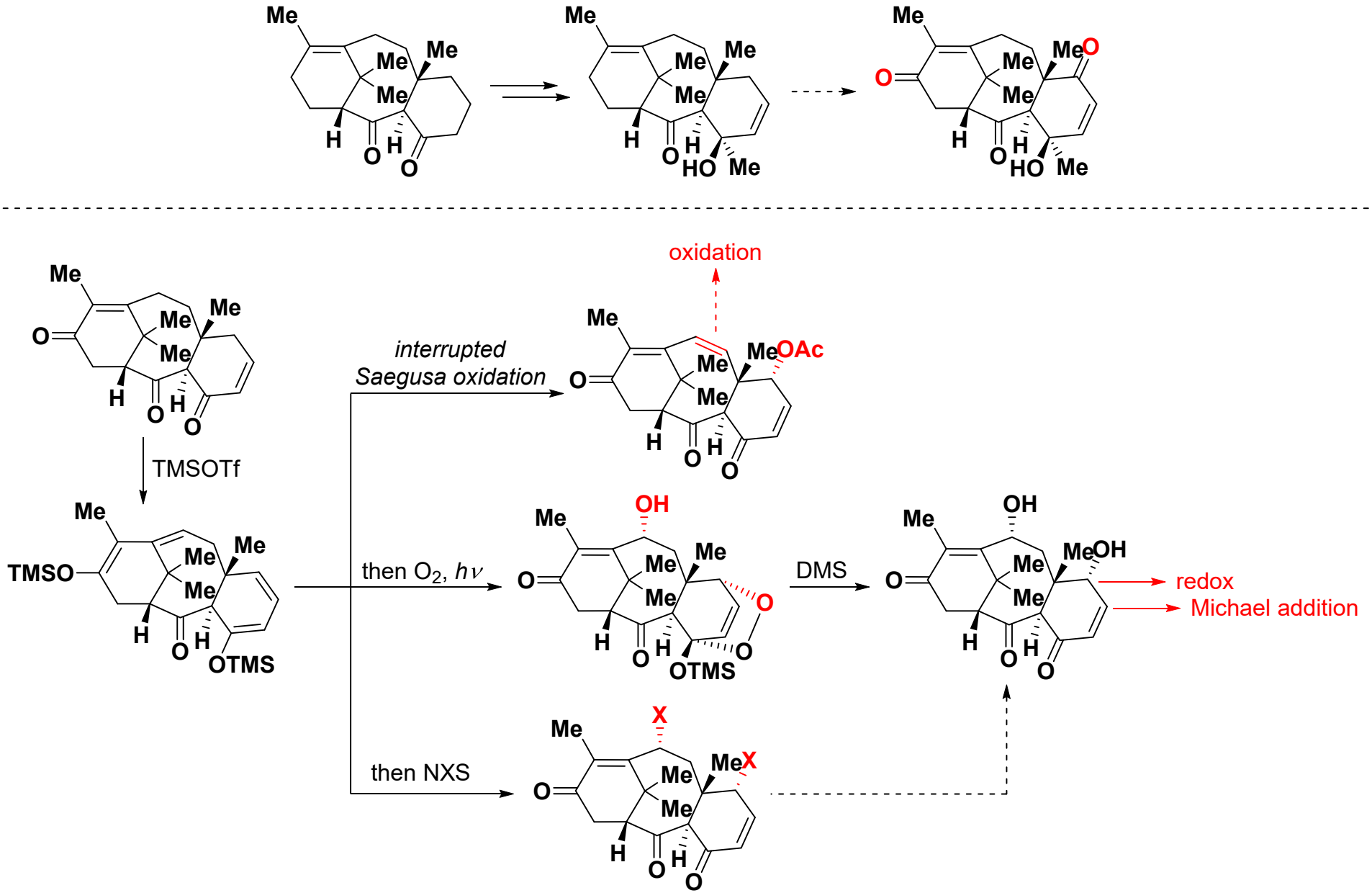
- C2-C5





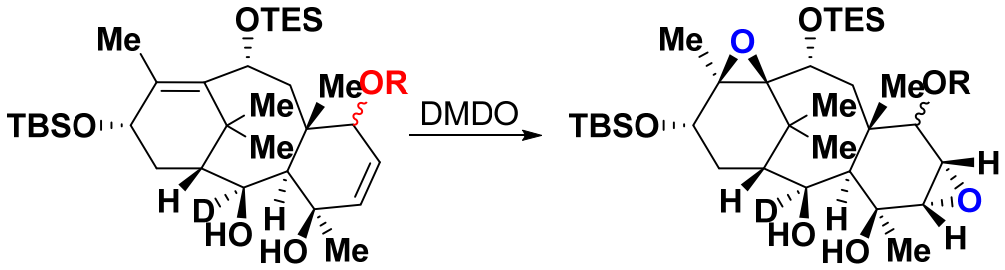
Kanda, Y.; Nakamura, H.; Umemiya, S.; Puthukanoori, R. K.; Appala, V. R. M.; Gaddamanugu, G. K.; Paraselli, B. R.; Baran, P. S. *J. Am. Chem. Soc.* **2020** *142*, 10526. Kanda, Y;. Ishihara, Y.; Wilde, N. C.; Baran, P. S. *J. Org. Chem.* **2020**, *85*, 10293.

Baran's work: two-phase synthesis

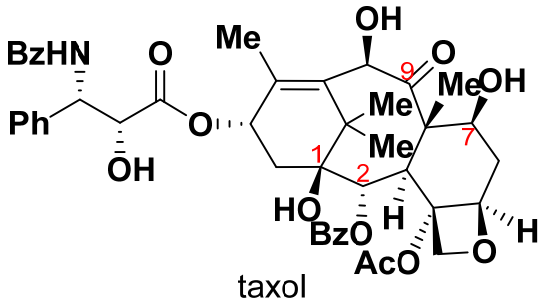


Kanda, Y.; Nakamura, H.; Umemiya, S.; Puthukanoori, R. K.; Appala, V. R. M.; Gaddamanugu, G. K.; Paraselli, B. R.; Baran, P. S. *J. Am. Chem. Soc.* **2020** *142*, 10526. Kanda, Y;. Ishihara, Y.; Wilde, N. C.; Baran, P. S. *J. Org. Chem.* **2020**, *85*, 10293.

Baran's work: two-phase synthesis



C1-C7



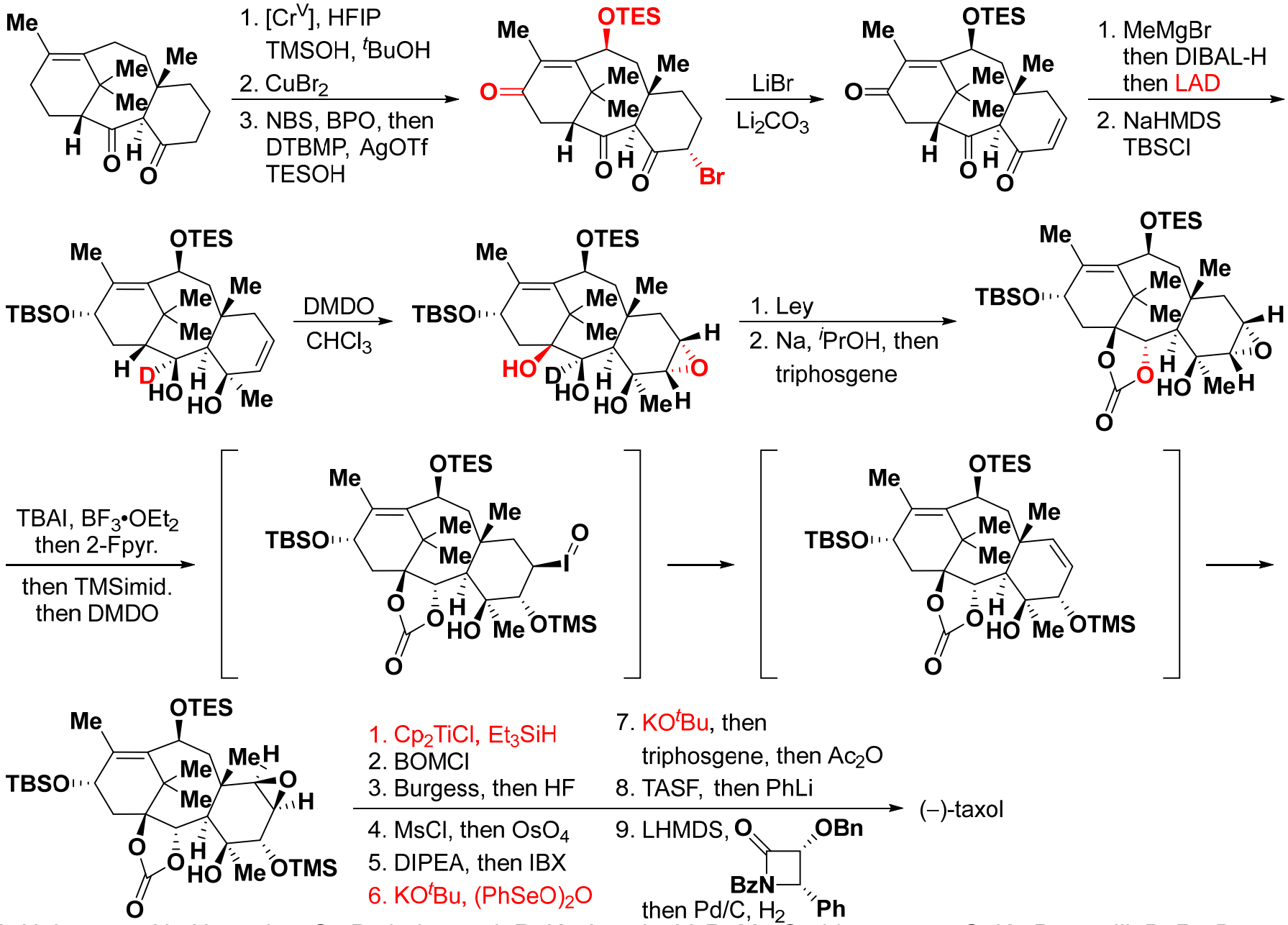
taxol

C1 C2: LAD, DMDO, Na
C9: at late stage in Holton's synthesis

C1-C2-C7-C9

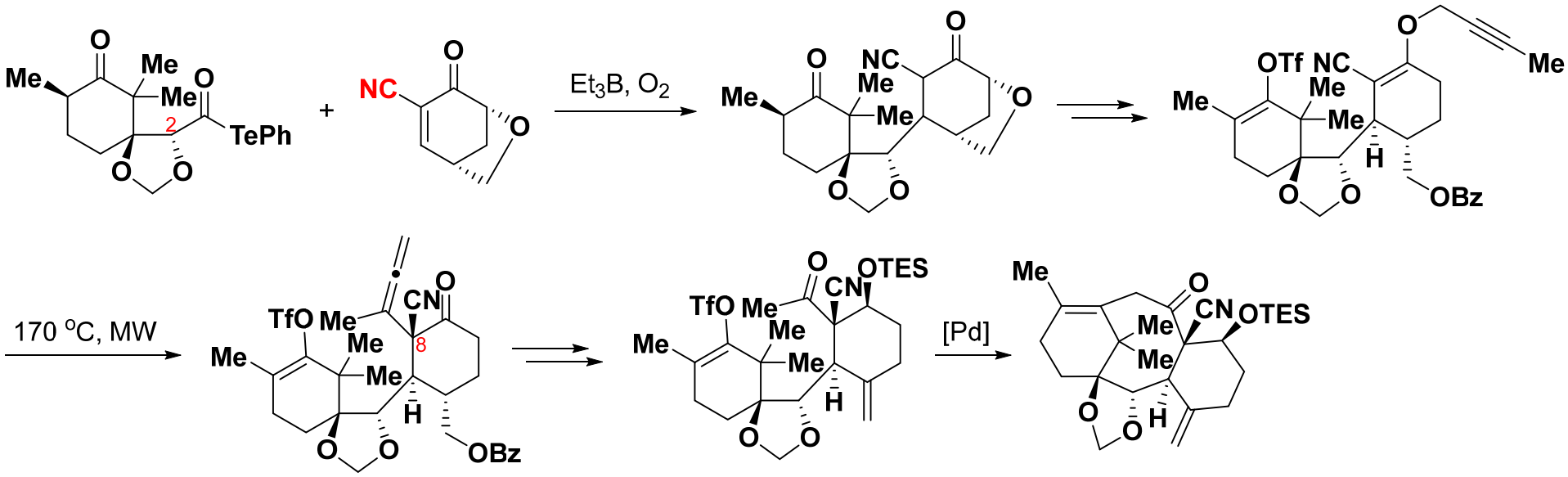
Kanda, Y.; Nakamura, H.; Umemiya, S.; Puthukanoori, R. K.; Appala, V. R. M.; Gaddamanugu, G. K.; Paraselli, B. R.; Baran, P. S. *J. Am. Chem. Soc.* **2020** *142*, 10526. Kanda, Y;. Ishihara, Y.; Wilde, N. C.; Baran, P. S. *J. Org. Chem.* **2020**, *85*, 10293.

Baran's work: two-phase synthesis



Kanda, Y.; Nakamura, H.; Umemiya, S.; Puthukanoori, R. K.; Appala, V. R. M.; Gaddamanugu, G. K.; Paraselli, B. R.; Baran, P. S. *J. Am. Chem. Soc.* **2020** *142*, 10526. Kanda, Y;. Ishihara, Y.; Wilde, N. C.; Baran, P. S. *J. Org. Chem.* **2020**, *85*, 10293.

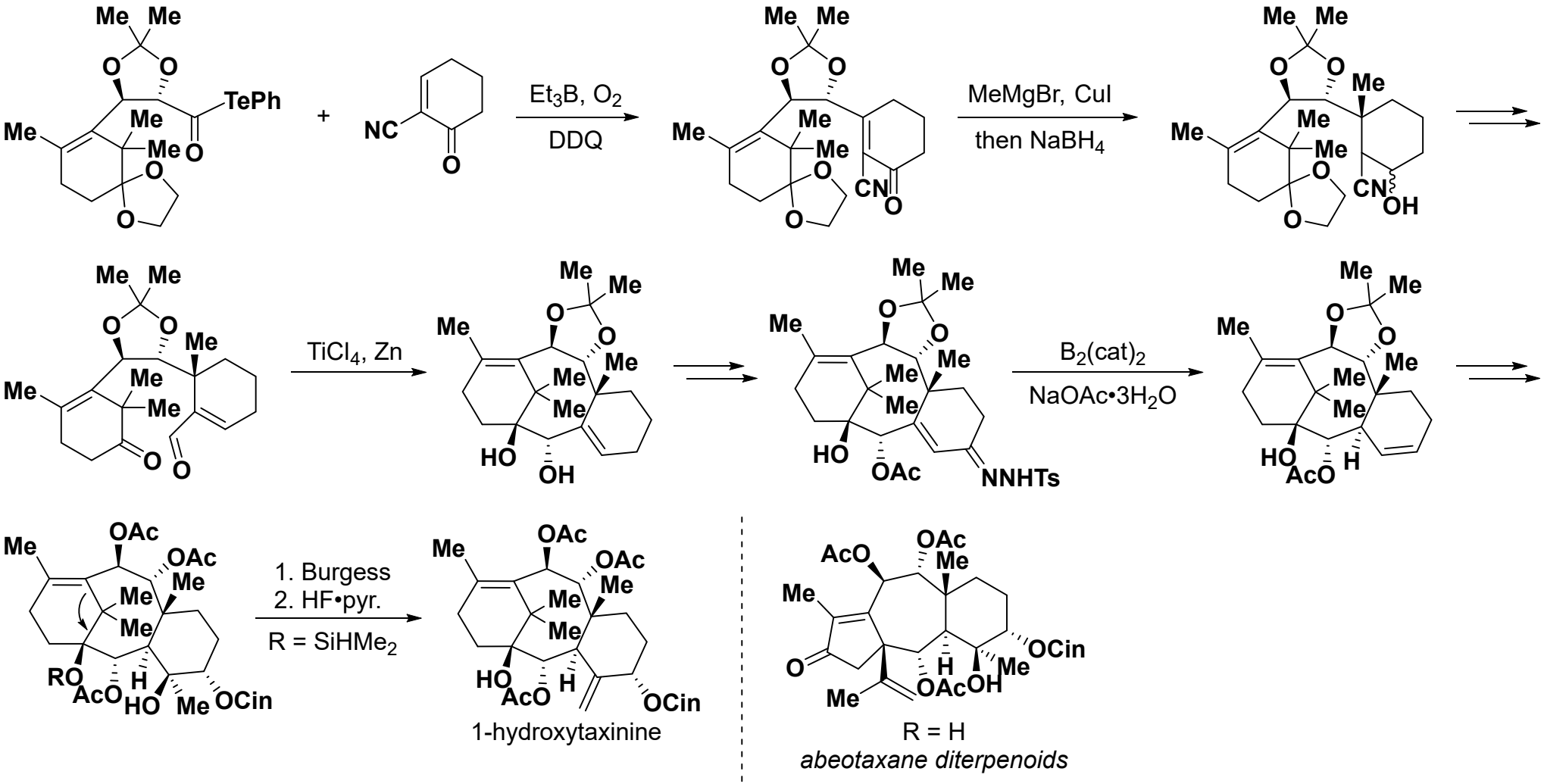
Inoue's work



- Chiral SM
- C2-C3 bond formation via radical coupling
- C2-stereochemical information
- Construction of C8 quaternary carbon centre via [3,3]
- C10-C11 bond formation via palladium chemistry

Matoba, H.; Watanabe, T.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2018**, *20*, 7554.

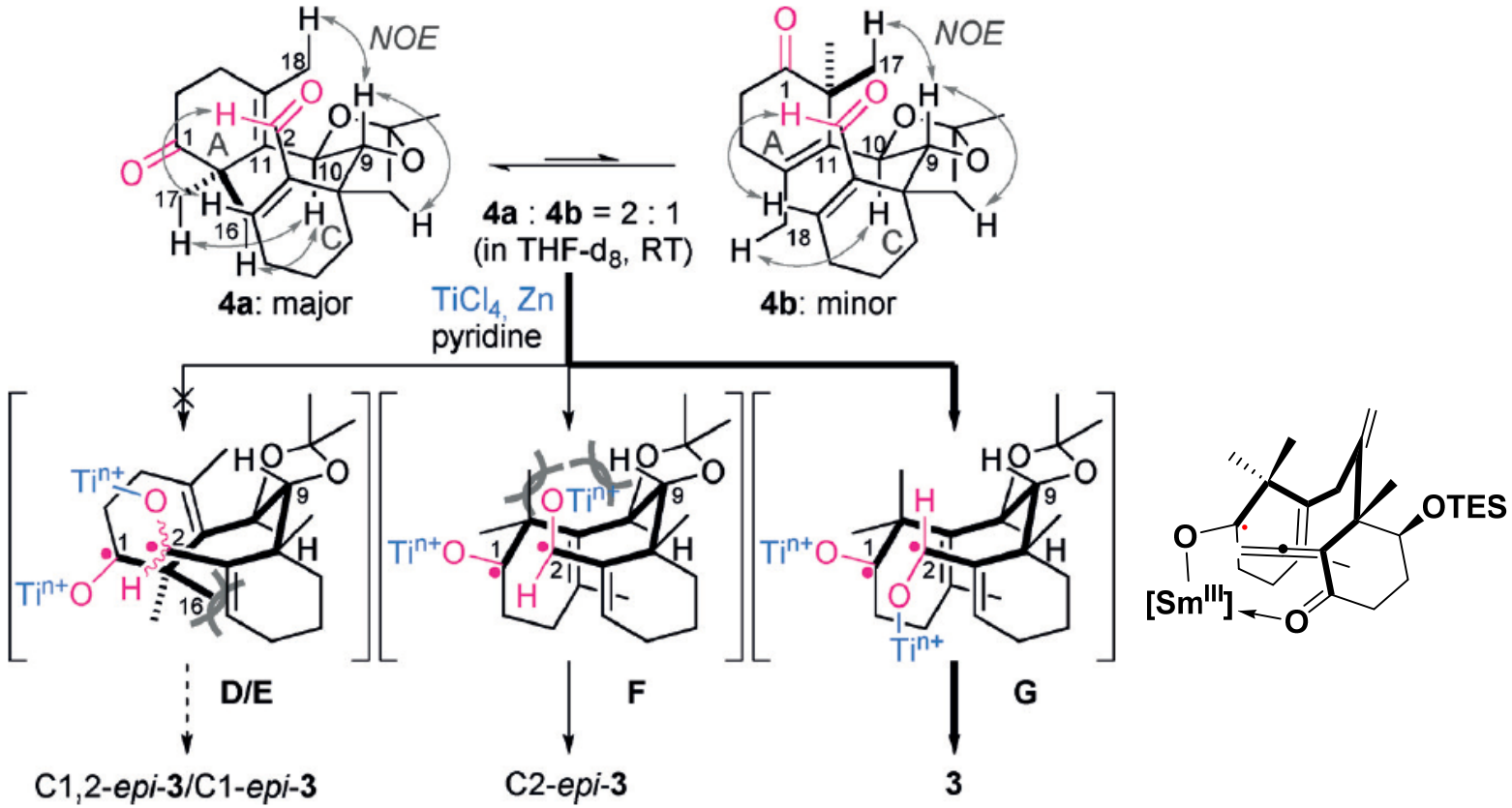
Inoue's work



- C8-C9 bond formation via radical coupling
- Construction of C8 quaternary carbon centre via conjugate addition
- C1-C2 bond formation via McMurry cyclization

Imamura, Y.; Yoshioka, S.; Nagatomo, M.; Inoue, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 12159.

Inoue's work



Imamura, Y.; Yoshioka, S.; Nagatomo, M.; Inoue, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 12159.

Contents

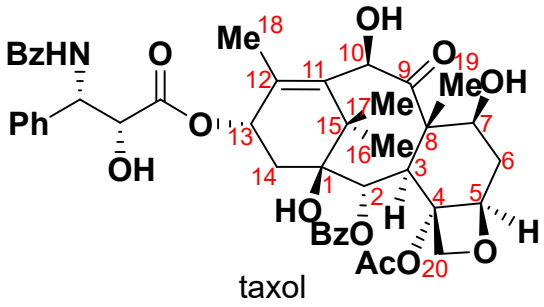
- ✓ **Introduction:** history, mechanism, classification, semi-synthesis & medicines

- ✓ **Selected strategies to construct taxane skeleton**
  - ➢ Biosynthesis & biomimetic synthesis
  - ➢ Diels-Alder
  - ➢ Miscellaneous

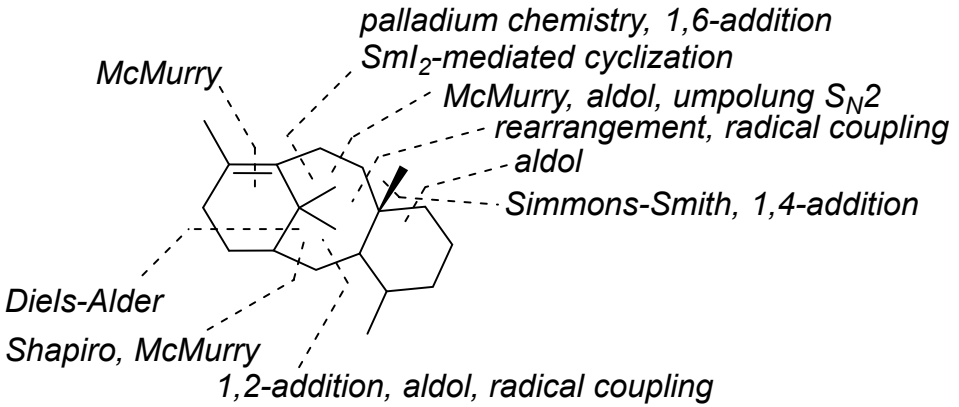
- ✓ **Total synthesis of taxol**

- ✓ **Summary**

Summary



taxol



positions	methods
C1	C2 enolate, epoxidation, DMDO
C5	allylic oxidation
C9 C10	enolate
C13	Cr chemistry
C20	dihydroxylation

Strategies: fragmentation, convergent synthesis, linear synthesis, two-phase synthesis