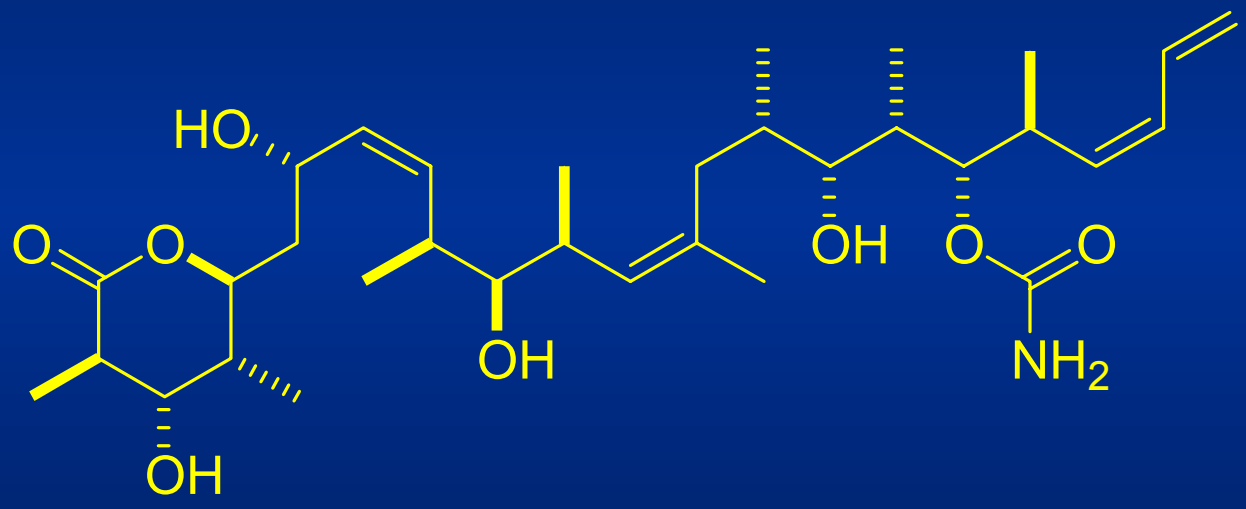
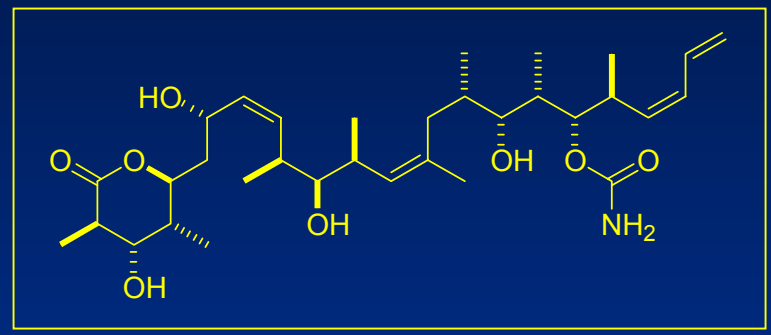
# The Chemistry and Biology of Discodermolide




Yueheng Jiang
November 20, 2003

# Outline




- Discovery and Biological Activity
- Total Syntheses
- Structure-Activity Relationships (SAR)

# Discovery

- Isolated by Gunasekera and co-workers in 1990 from the Caribbean deep-sea sponge (*Discodermia dissoluta*).
- 0.002% w/w isolation yield (7 mg/434 g of sponge).
- Found initially to have immunosuppressive and antifungal activities.
- Further revealed to be a potent microtubule stabilizer.

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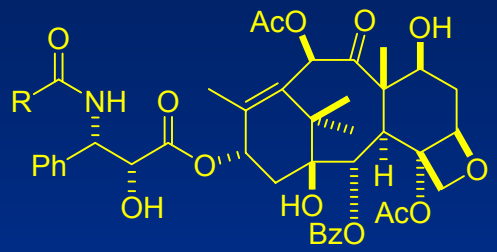
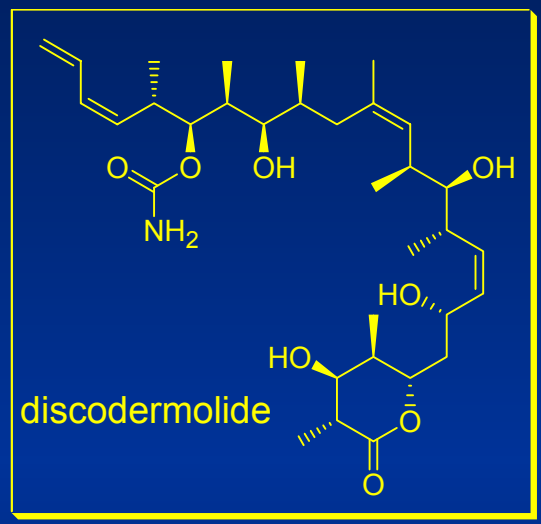
Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem*. **1991**, *56*, 1346.
Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekera, M.; Gunasekera, S. P.; *Transplantation* **1991**, *52*, 650.
ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243.

# Microtubule-stabilizing agents

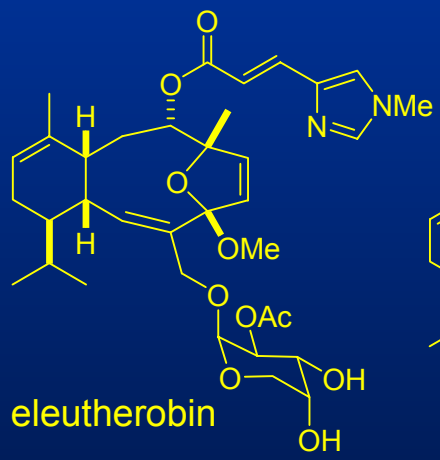



R = Ph Taxol (BMS)
R = O*t*Bu Taxotere (Aventis)

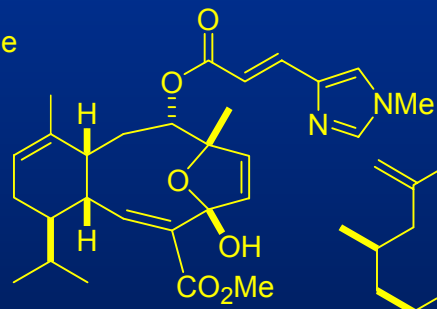



discodermolide

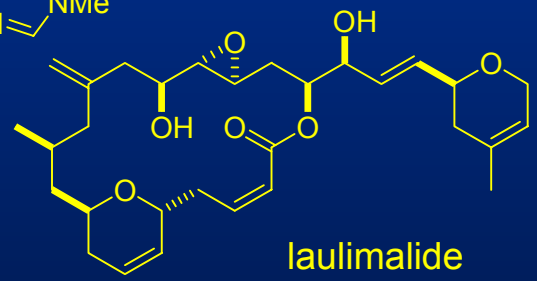

R = H epothilone A
R = Me epothilone B




eleutherobin




sarcodictyin A




laulimalide

# Cytotoxicity

- Cytotoxic over a variety of cell lines ($IC_{50}$ 3-80 nM)
- More potent than Taxol
- Competitively inhibits the binding of Taxol to tubulin
- Active against multi-drug resistant (MDR) and Taxol-resistant (Pgp mediated MDR) cell lines

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ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243.
Kowalski, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E.; *Mol. Pharmacol*. **1997**, *52*, 613.

# Mechanism of action

- Promote tubulin polymerization *in vitro*
- Stabilize microtubules against depolymerization
- Interfere with Taxol-binding to microtubules
- Induce microtubule bundles in cells

Consequences:

Interfere with proper formation of mitotic spindle

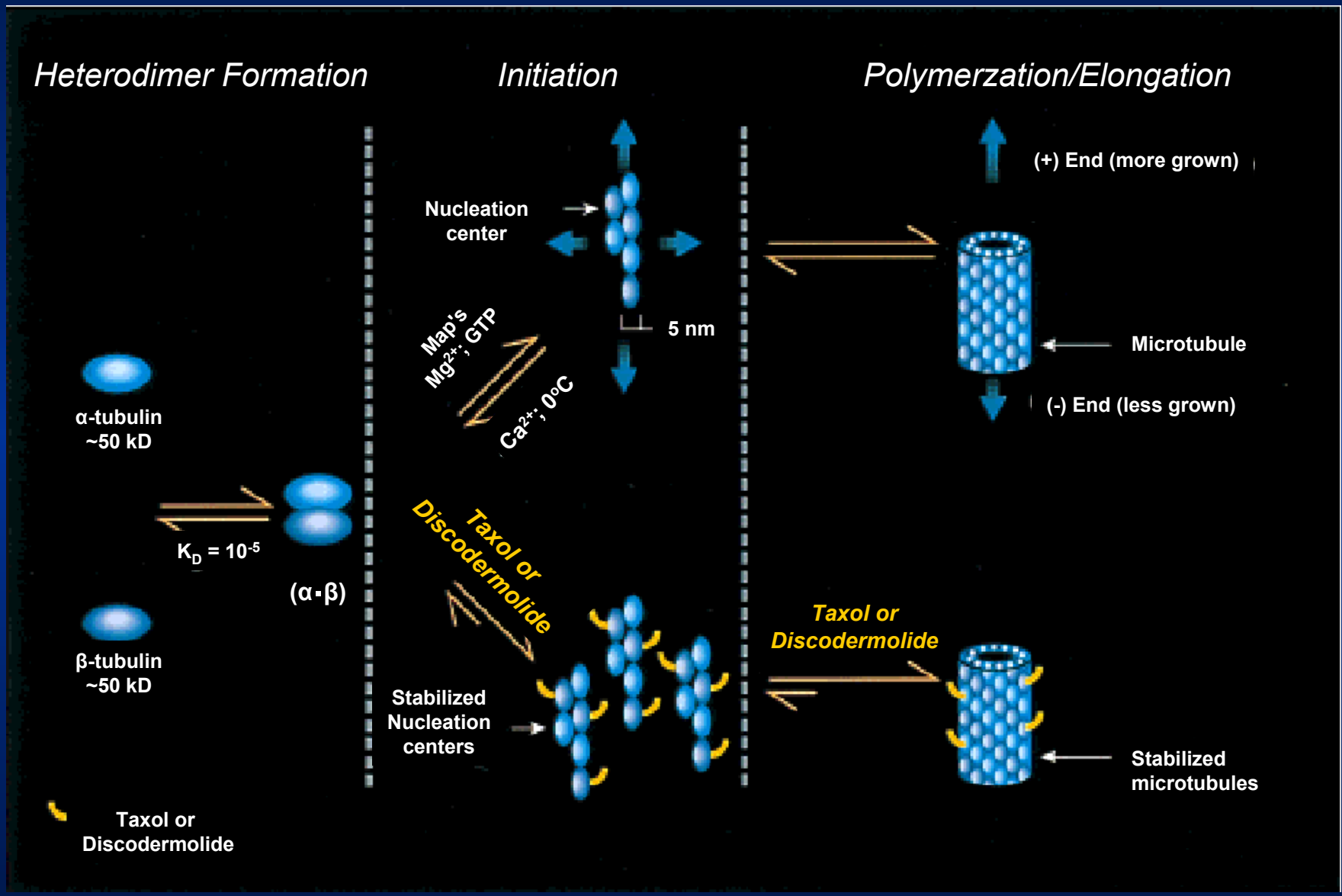
↓

Cause arrest of cell cycle

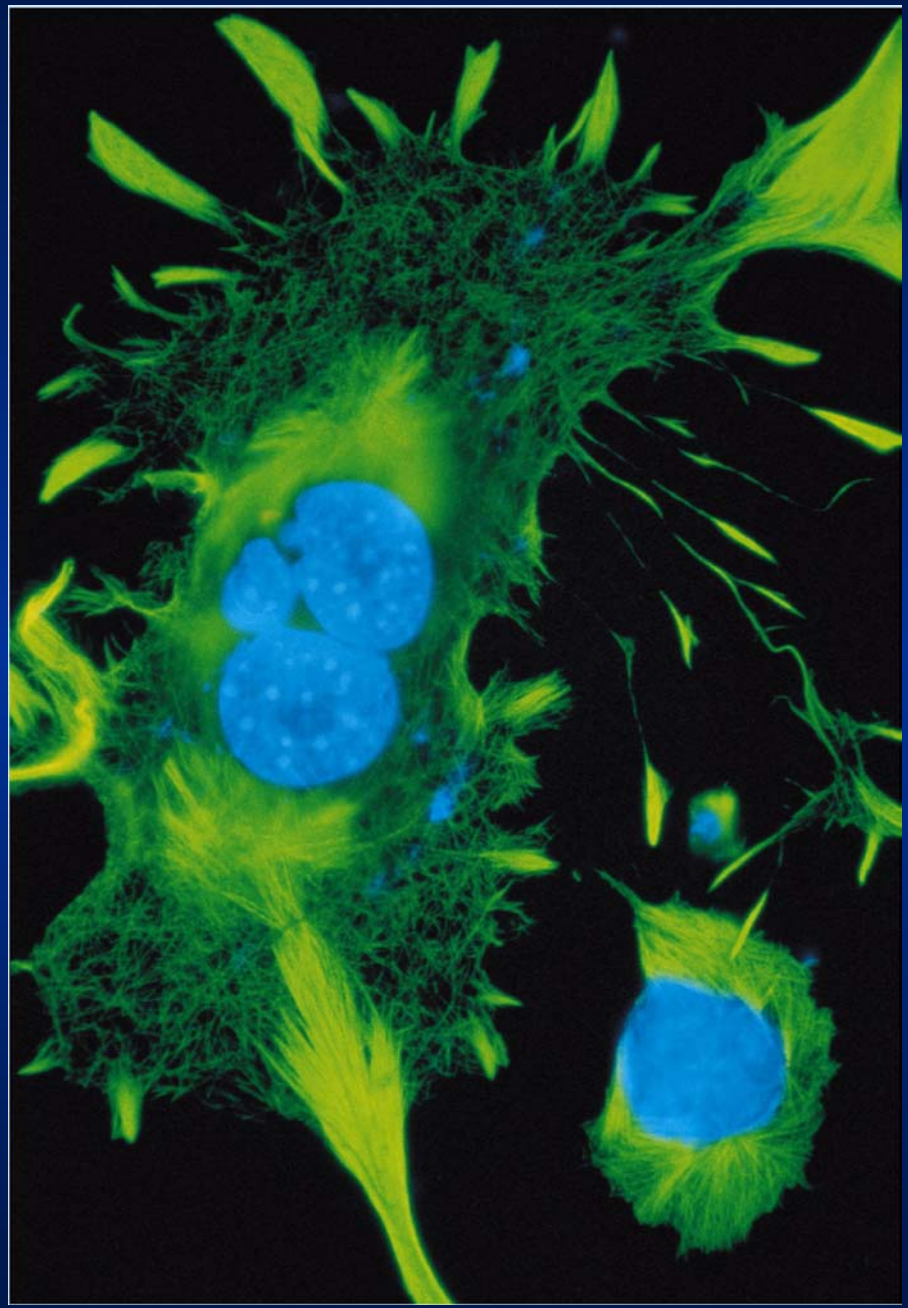
↓

Cell death by apoptosis

# Dynamic Equilibria of Tubulin-Microtubules




Nicolaou, K. C.; Roshangar, F.; Vourlounis, D. *Angew. Chem. Int. Ed.*, **1998**, *37*, 2014.



# Microtubule Bundling

Influence of discodermolide on a transformed mouse fibroblast.

Discodermolide induces microtubule bundling (tubulin appears green), which is clearly seen in the pseudopodia and near the nucleus (appears blue). As a result of this microtubule bundling, the cell is undergoing apoptosis and fragmentation of the nucleus can be seen.

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Sasse, F. *Current Biology,* **2000**, *10*, R469.

# Unique Activities

- Discodermolide could not substitute for Taxol in a Taxol-resistant cell line (A549-T12) that requires low concentrations of Taxol for normal growth.

- Exhibits synergistic effects with Taxol in several cultured cell lines (not observed with Taxol/epothilones or Taxol/eleutherobin).

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Martello, L. A.; McDaid, H. M.; Regl, D. L.; Yang, C. H.; Ment, D. T.; Pettus, R. R.; Kaufman, M. D.; Arimoto, H.; Danishefsky, S. J.; Smith, A. B. III; Horwitz, S. B. *Clin. Cancer Res*. **2000**, *6*, 1978.
Giannakakou, P.; Fojo, T. *Clin. Cancer Res*. **2000**, *6*, 1613.

# Potential Candidate for Cancer Chemotherapy

- Novel structure
- Greater or comparable efficacy to Taxol
- Poor substrate for P-glycoprotein (Pgp).
- Synergistic effect in combination with Taxol
- Greater water solubility (100-fold > Taxol)

Entered Phase I clinical trials in 2002 as a chemotherapeutic agent for use against solid tumors.

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Myles, D. C. *Annual Reports in Med. Chem.*, **2002**, *37*, 125.

- Taxol (semi-synthesis)
- Epothilone (fermentation)
- Discodermolide ( ???)

## Total Synthesis of Discodermolide !

(-)-Discodermolide

S. L. Schreiber (1993)
A. B. Smith (1995)
D. C. Myles (1997)

(+)-Discodermolide

S. L. Schreiber (1996)
J. A. Marshall (1998)
A. B. Smith (1999, 2003)
I. Paterson (2000, 2002)
Novartis (2003)
D. C. Myles (2003)

# Selected Total Synthesis of (+)-Discodermolide

## Schreiber

1st total synthesis of (+/-)-discodermolide
established absolute configuration

## Smith

Delivered ~1 g of (+)-discodermolide (2nd generation)

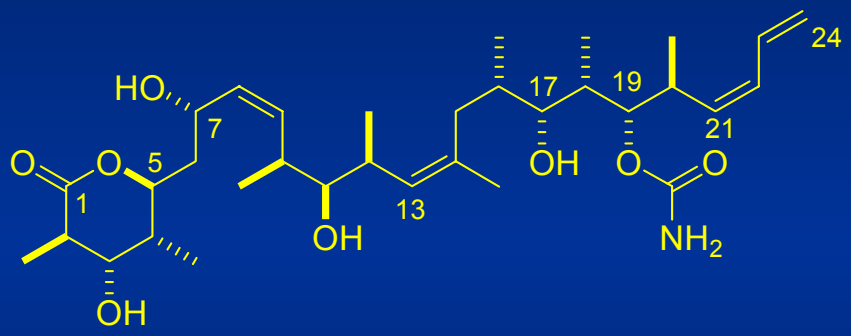
## Paterson

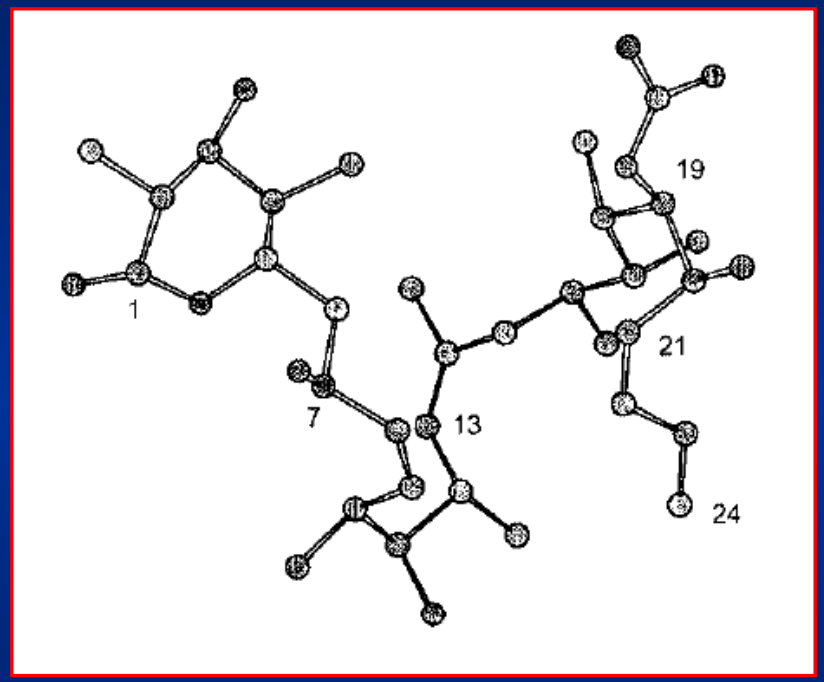
Novel approaches

## Novartis

Meet supply needs for clinical studies by total synthesis

# Structure and conformation of (+) discodermolide

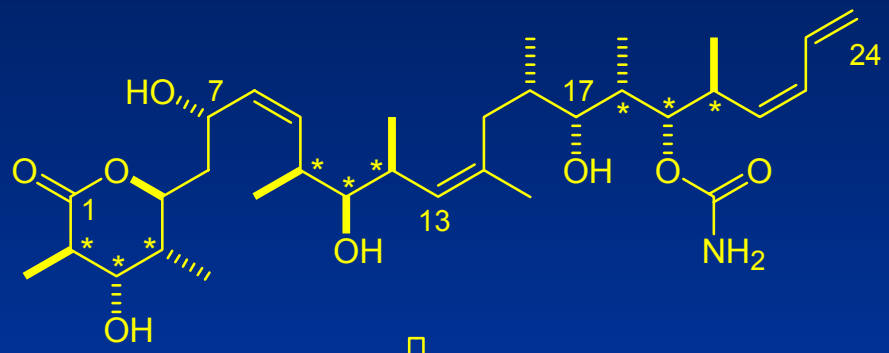


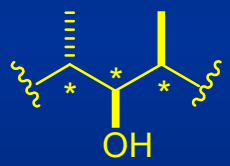




X-ray structure of discodermolide; hydrogen atoms omitted for clarity

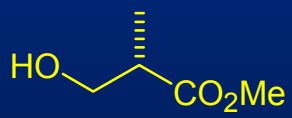
Paterson, I.; Florence, G. J. *Eur. J. Org. Chem.*, **2003**, 2193.

# General Features




repeating *anti*, *syn*-stereotriad



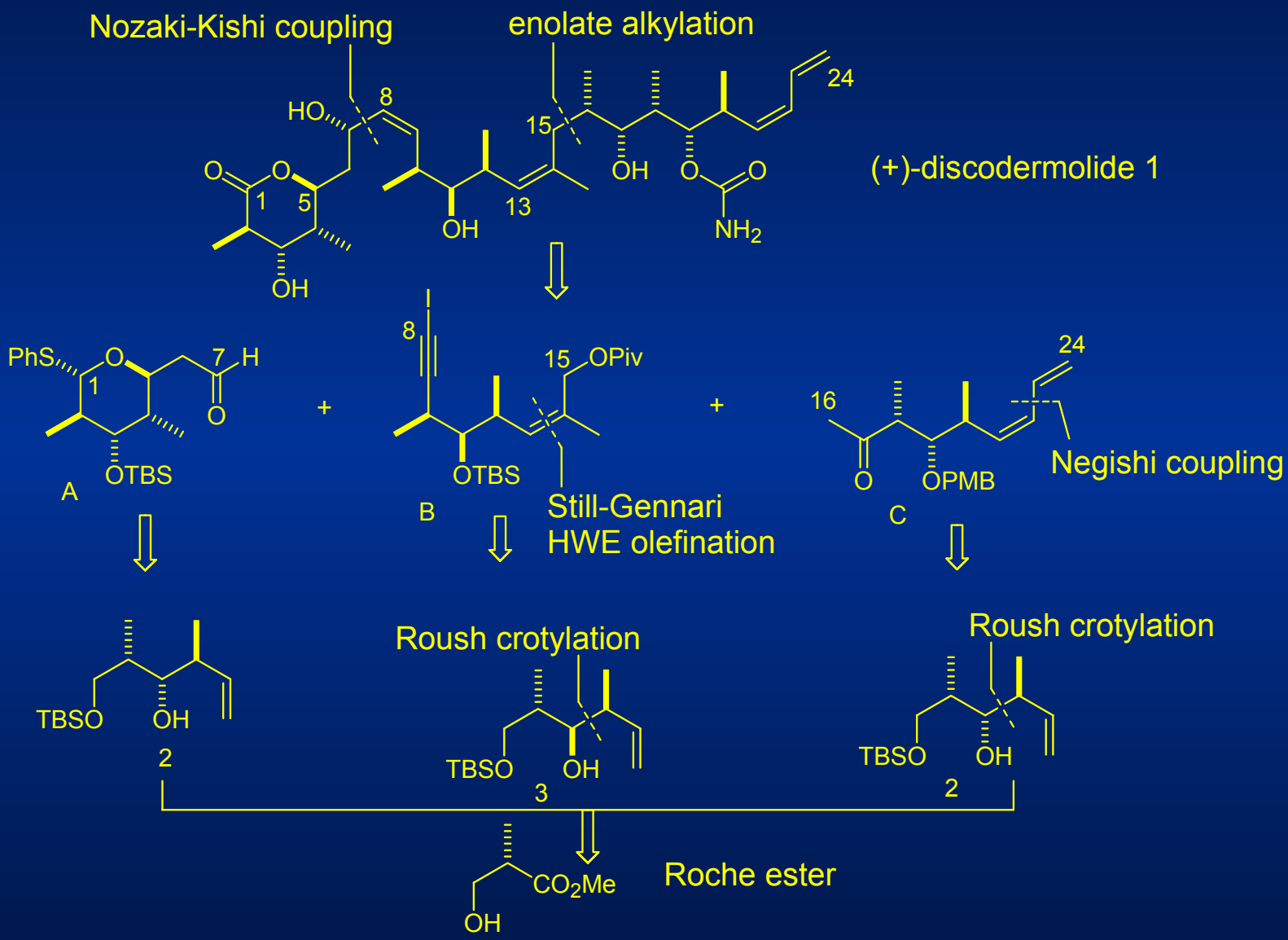

Roche ester

divided into three fragments of roughly equal complexity

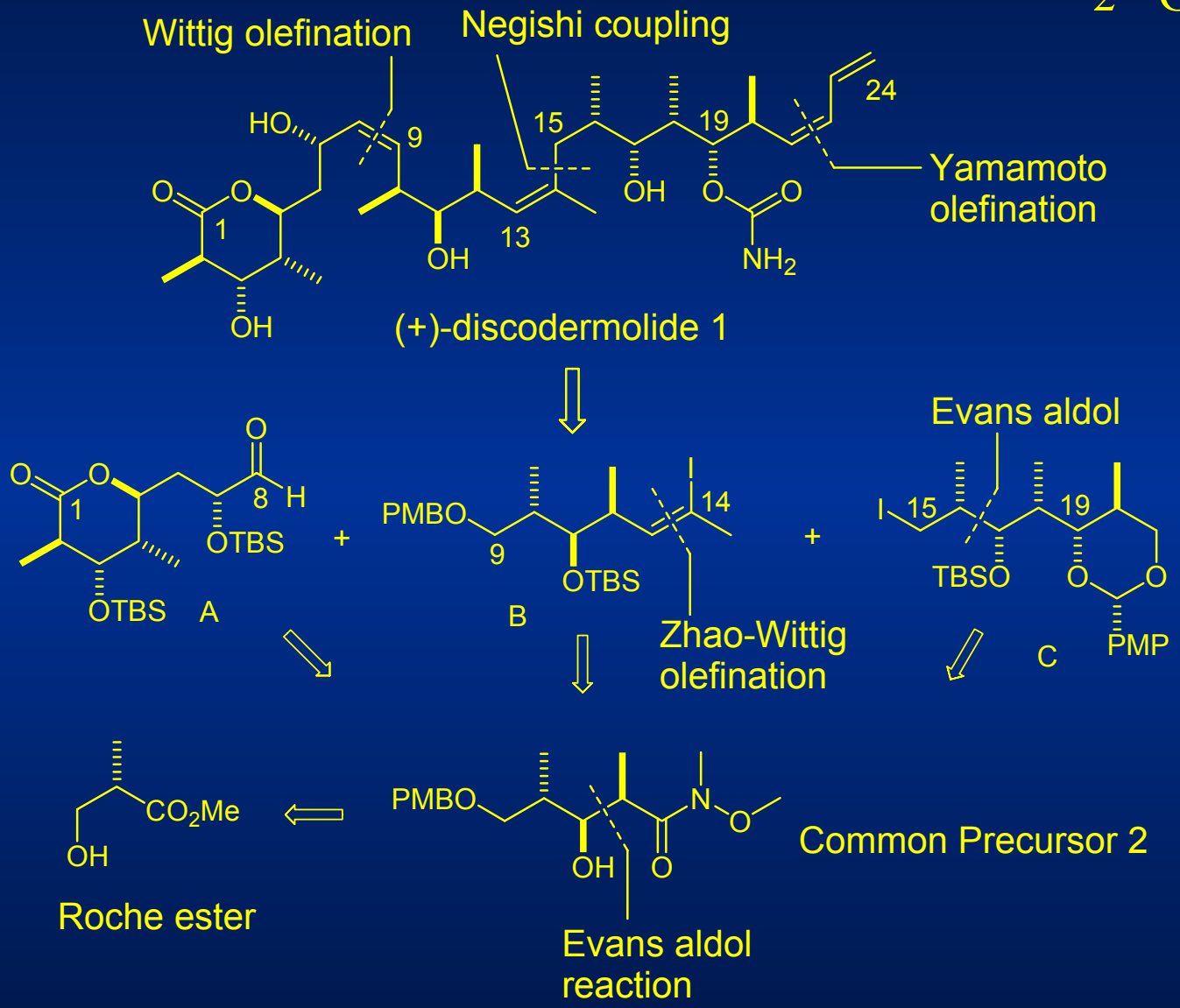
Fragment Coupling

Introduction of two Z-alkenes and terminal Z-diene

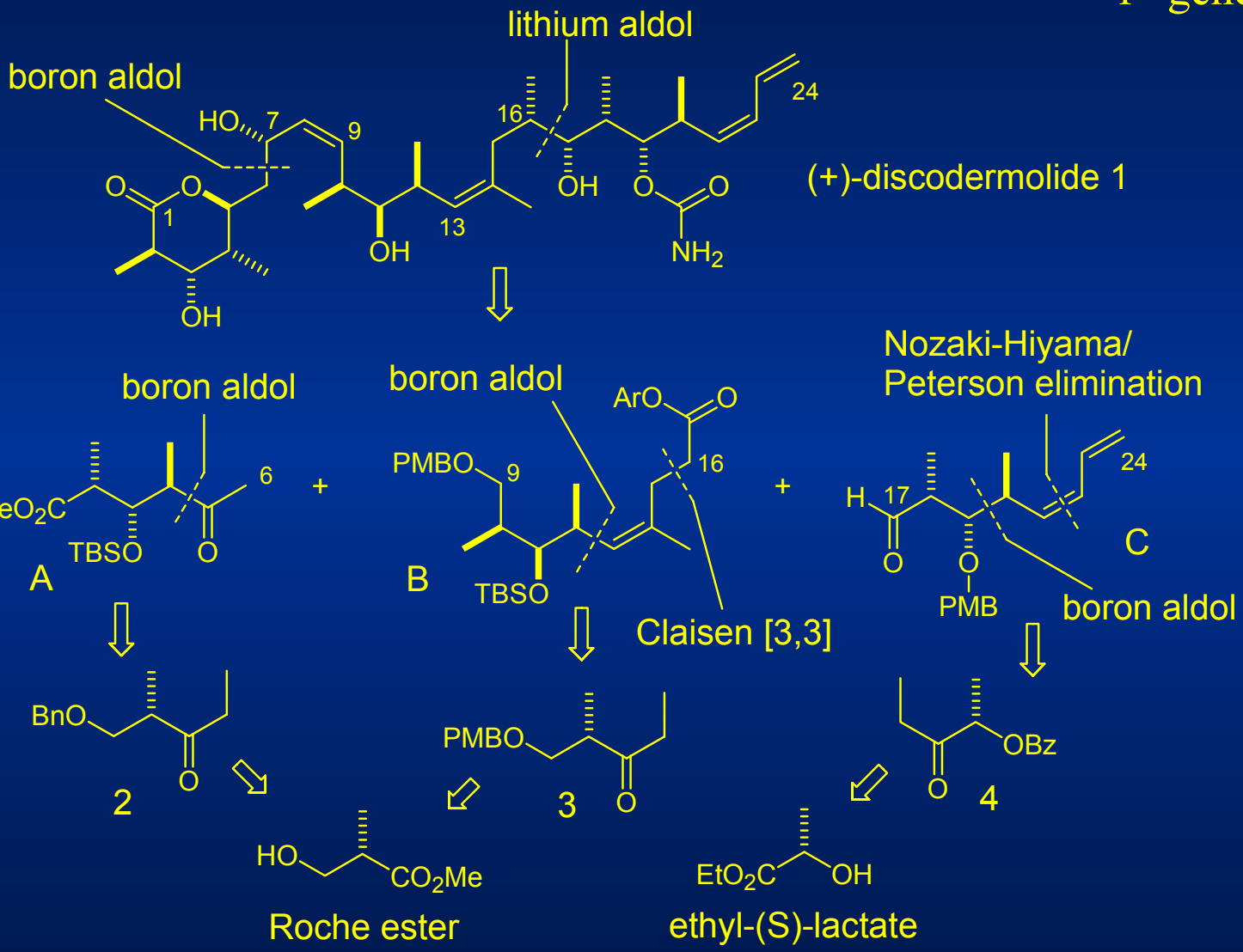
# Strategy by Scheiber



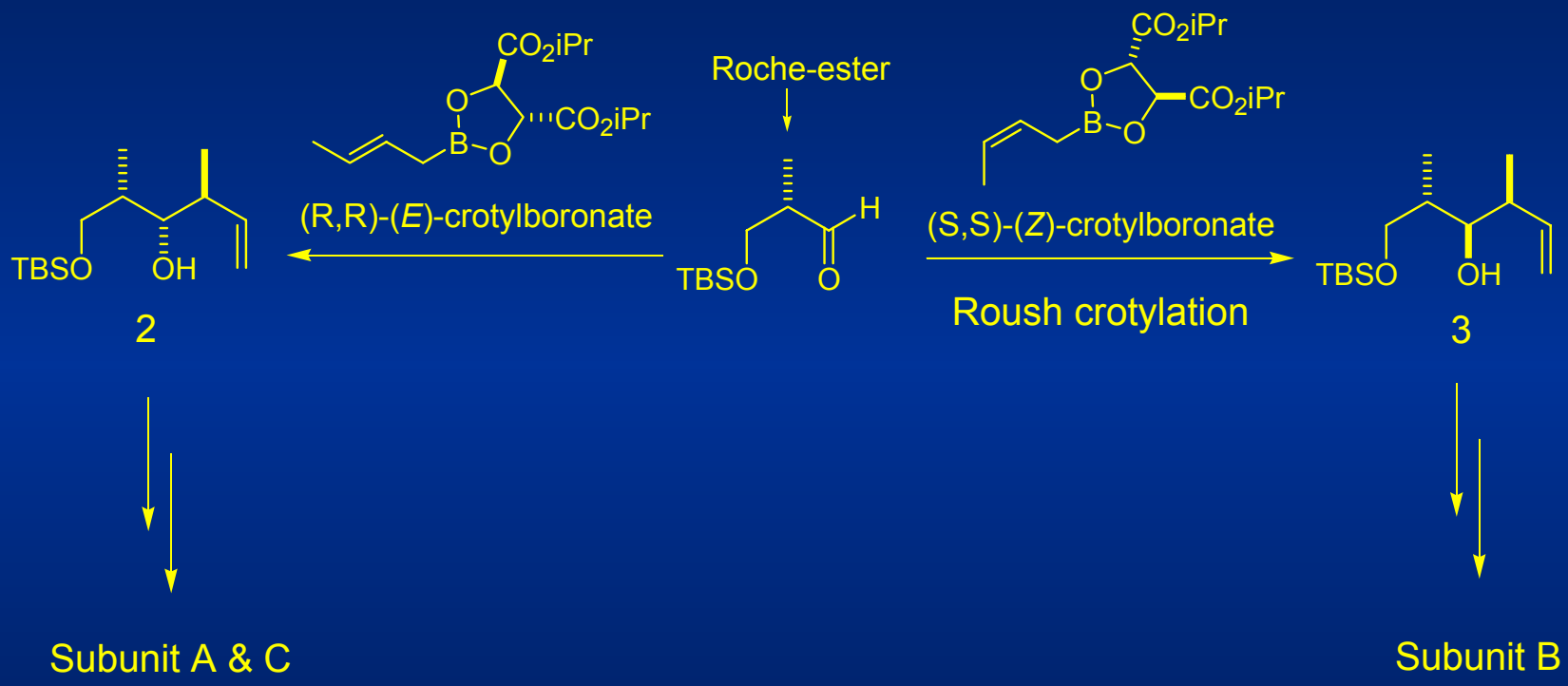
# Strategy by Smith
# 2nd Generation



# Strategy by Paterson
# 1st generation



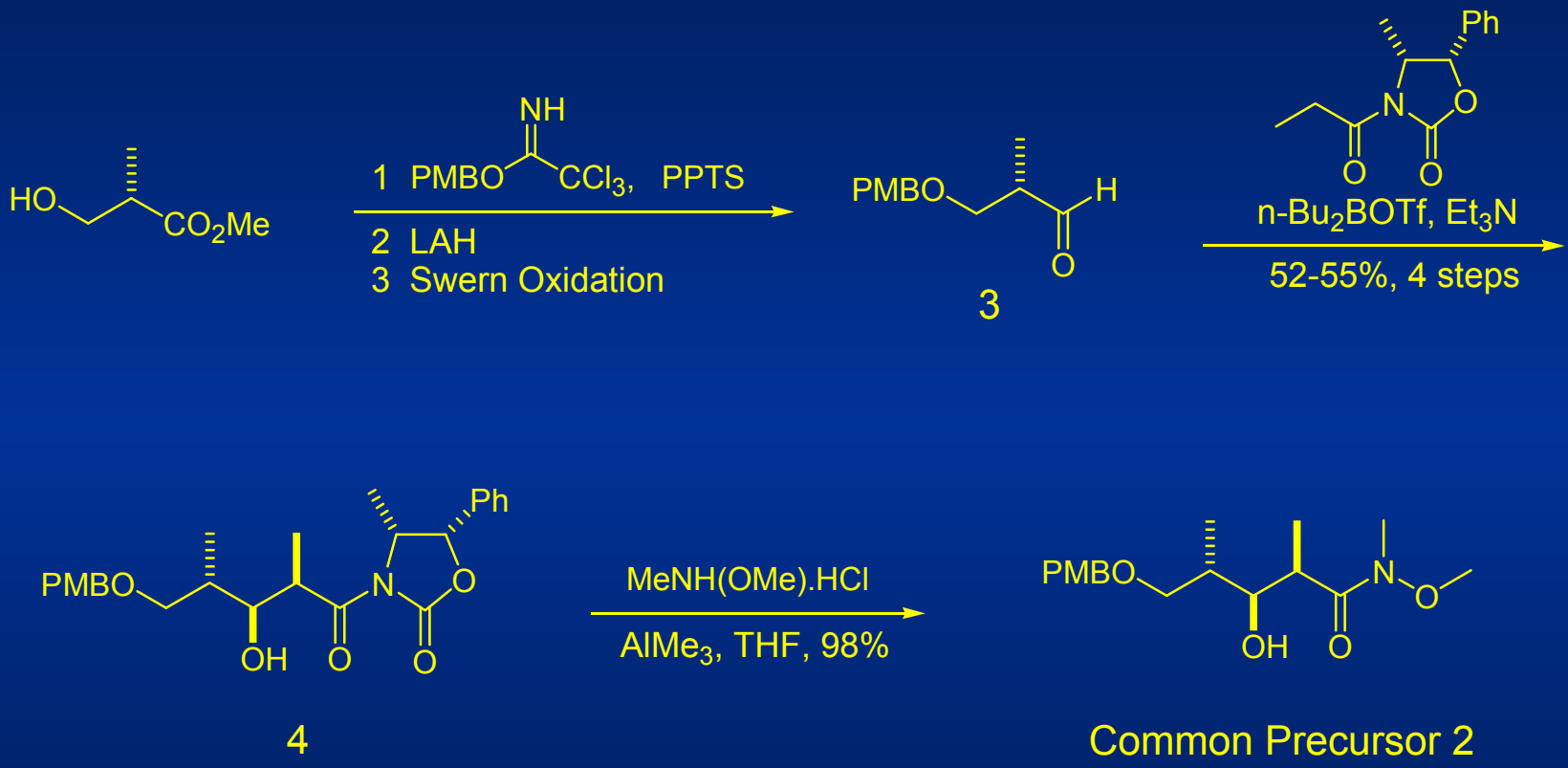
# Synthesis of Stereotriad by Schreiber





Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054.
Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc*. **1990**, *112*, 6348.

# Synthesis of stereotriad by Smith



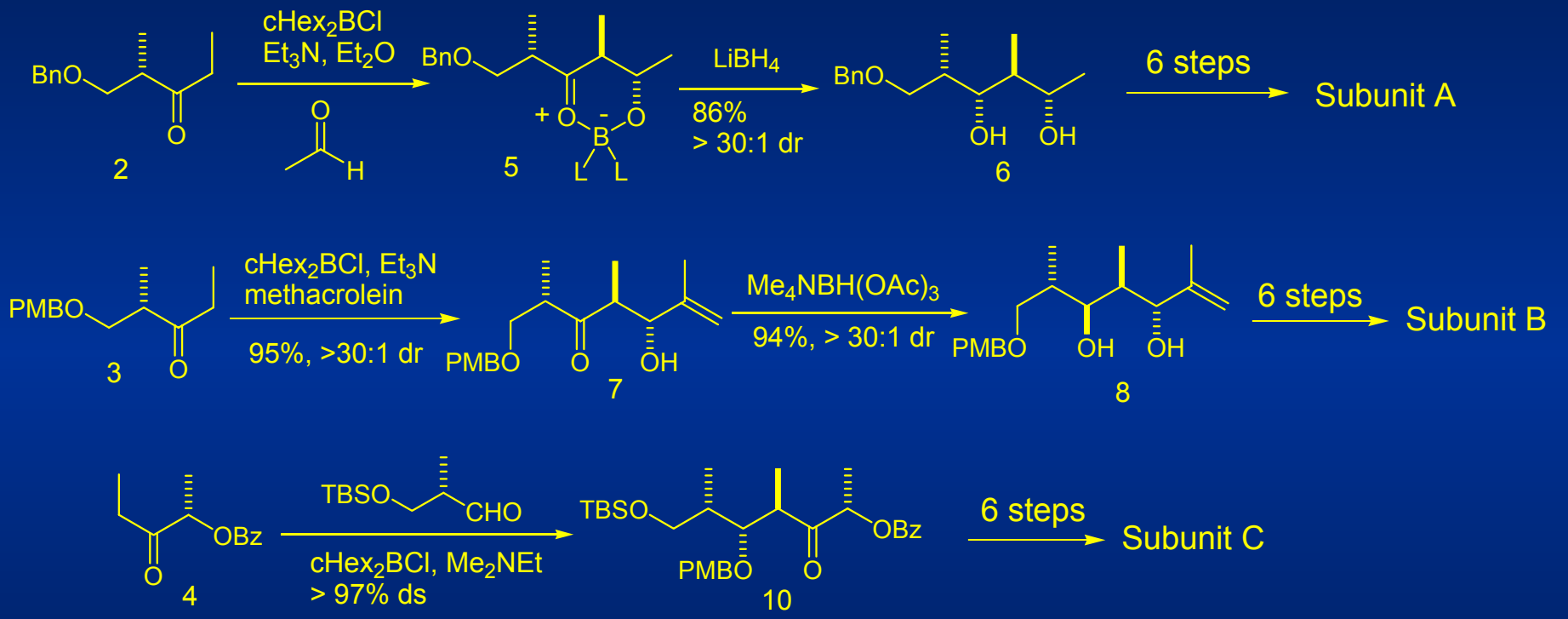


Smith, A. B. III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc*. **2000**, *122*, 8654.

Smith, A. B. III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett*. **1999**, *1*, 1823.

Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun*. **1981**, 1240.

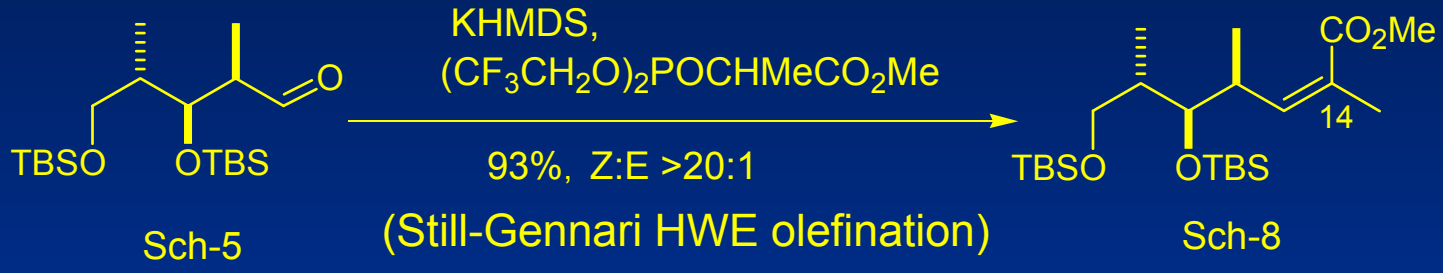
# Synthesis of stereotriad by Paterson



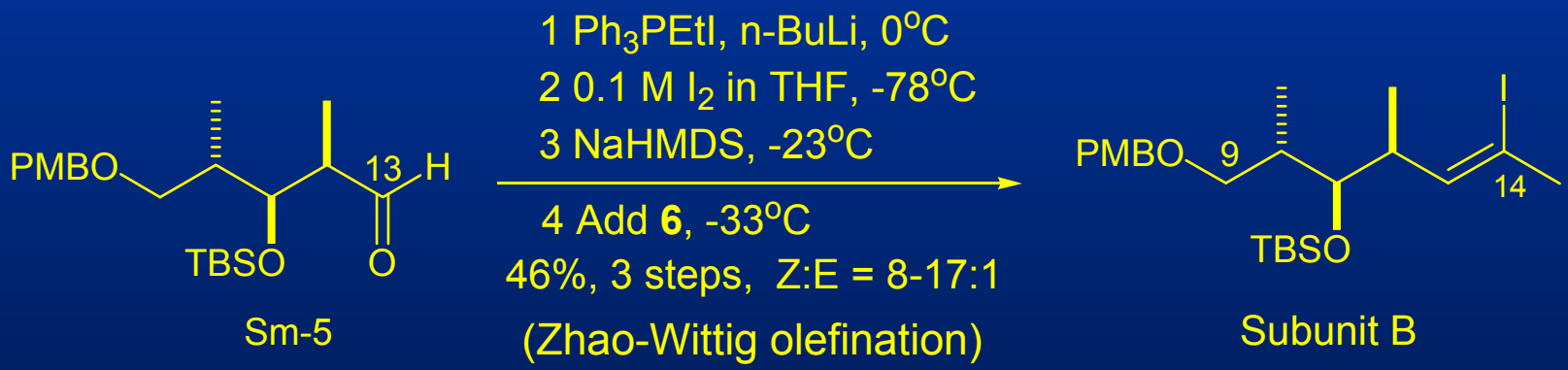


Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem. Int. Ed.* **2000**, 39, 377.
Paterson, I.; Arnott, E. A. *Tetrohedron Lett.* **1998**, 39, 7185.
Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639.

## Schreiber




## Smith

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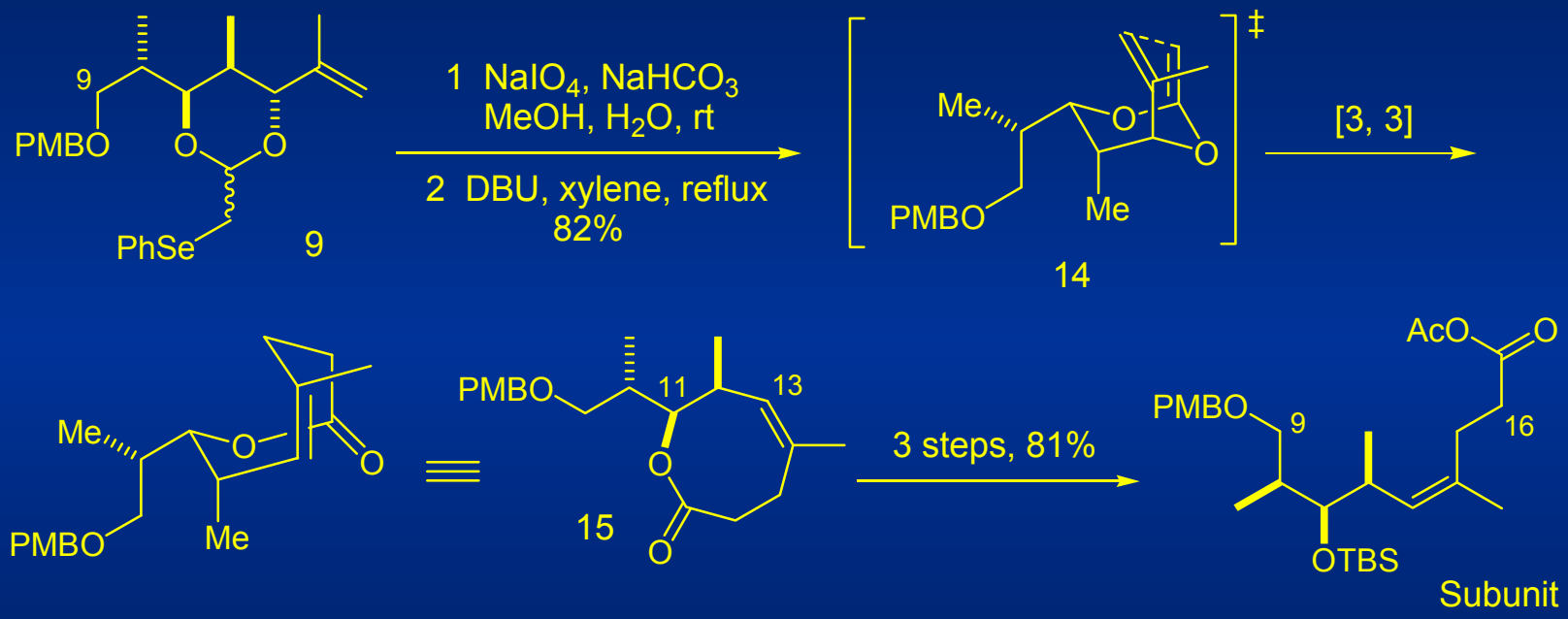
Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405.
Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett*. **1994**, *35*, 2827.

# Synthesis of trisubstituted (Z)-alkene

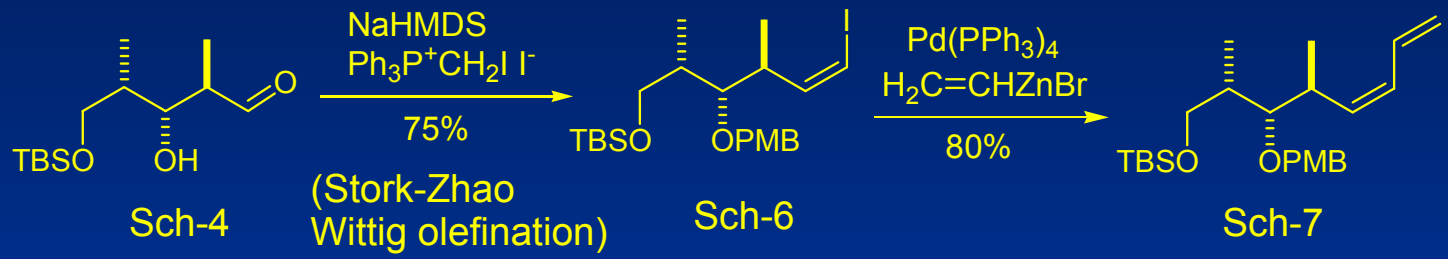
Paterson




Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483.

# Synthesis of terminal (Z)-diene

## Schreiber



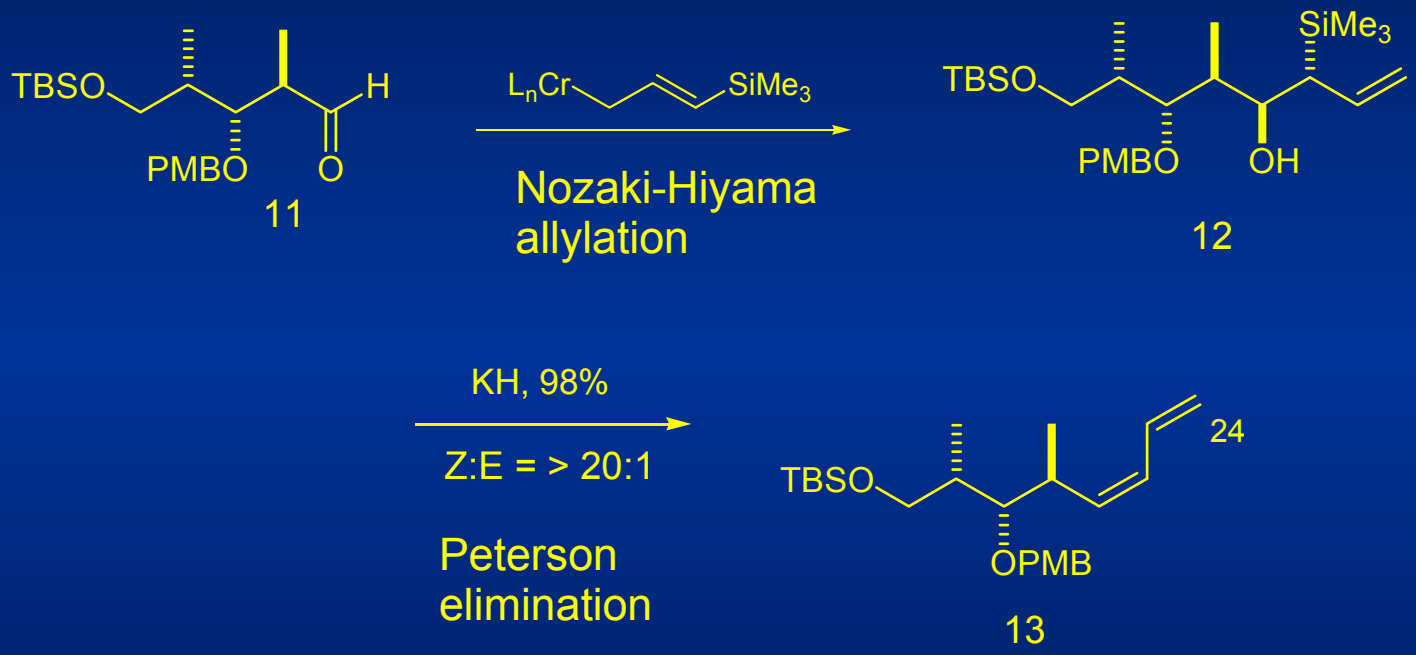

## Smith



1. Stock, G.; Zhao, K. *Tetrahedron Lett*. **1989**, *30*, 2173.
Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 723.

# Synthesis of terminal (Z)-diene

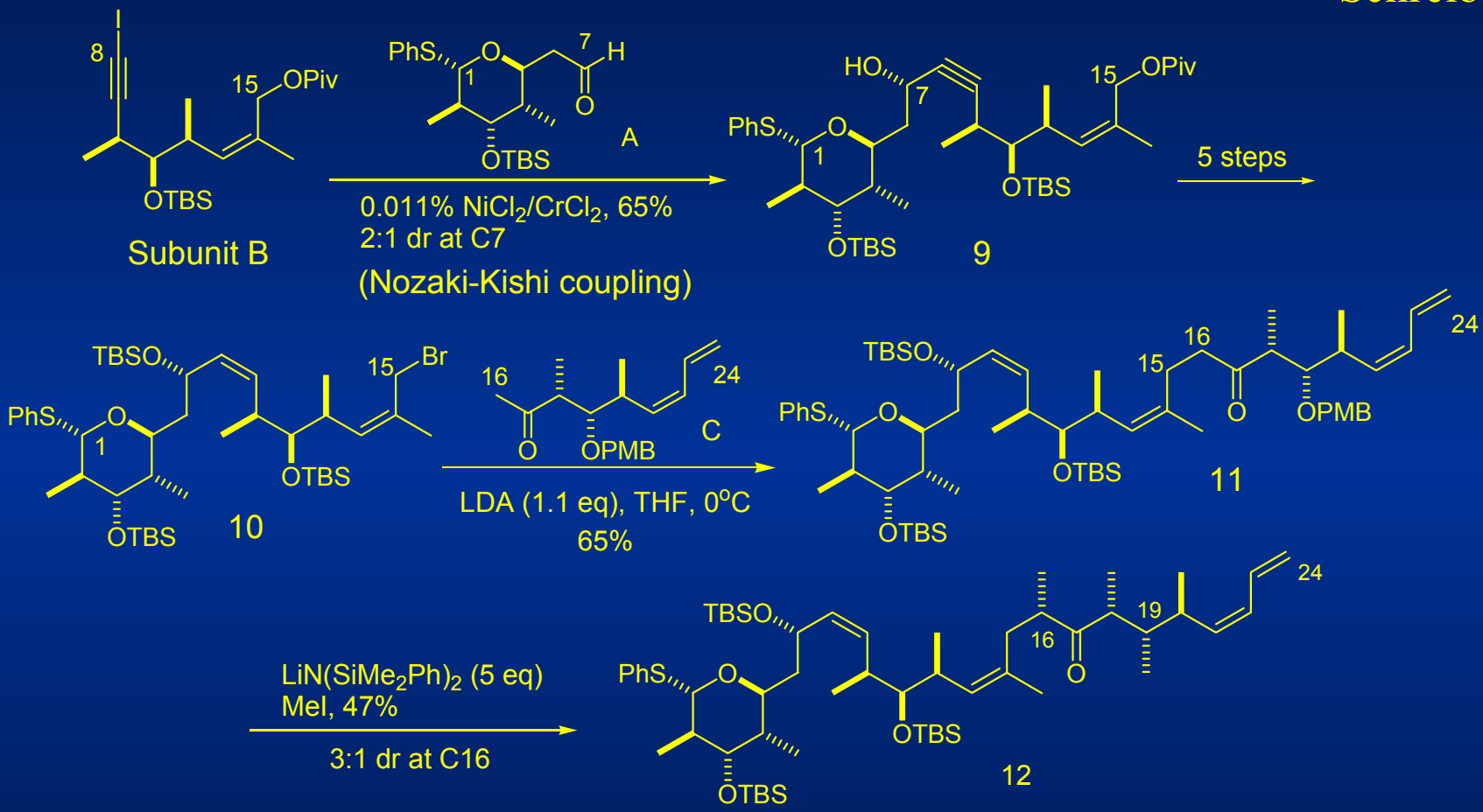
Paterson





Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1985**, *26*, 5585.
Aicher, T. D.; Kishi, Y. *Tetrahedron Lett*. **1987**, *28*, 3463.
Ager, D. *Org. React*., **1990**, *38*, 1.

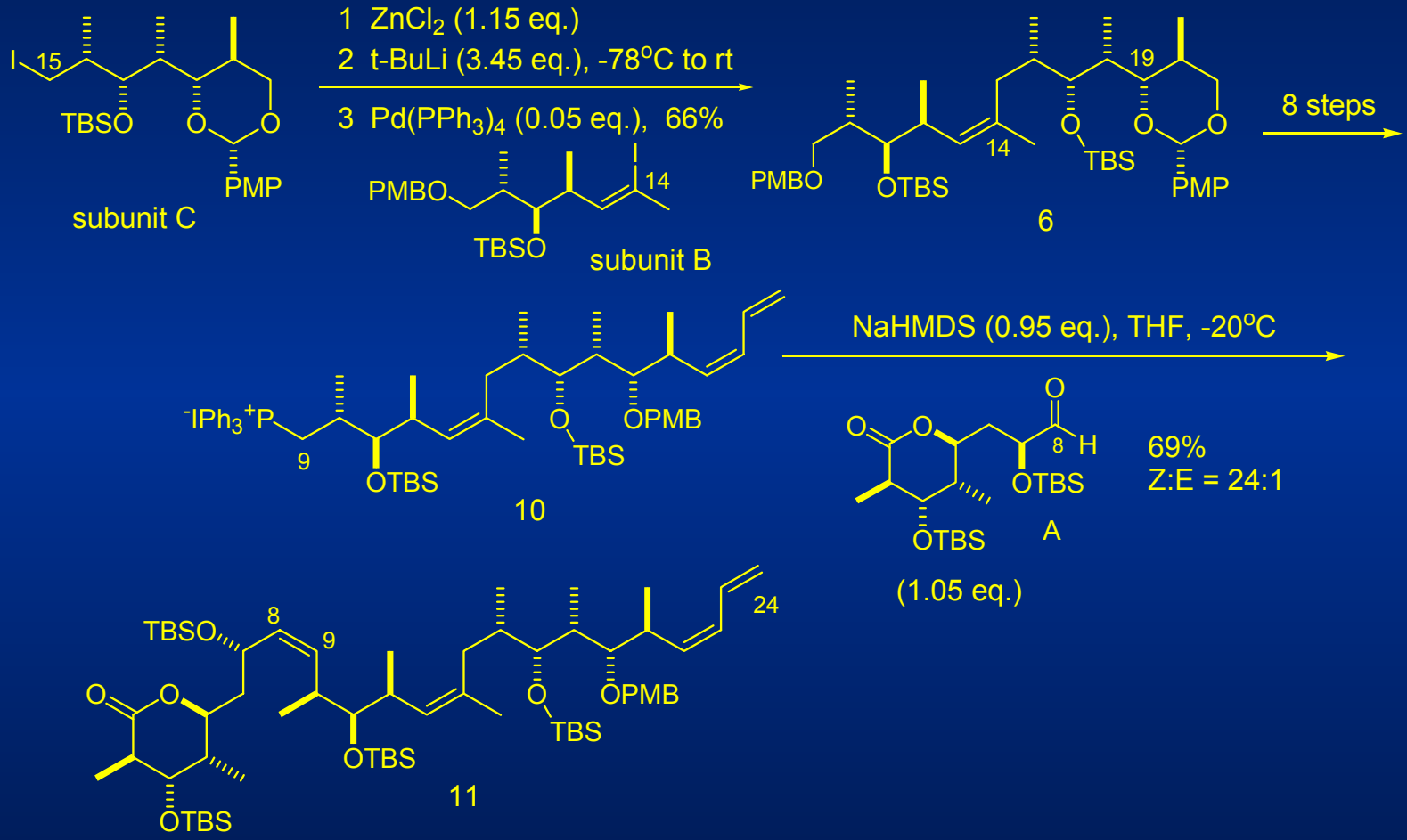
# Fragment coupling
# Schreiber



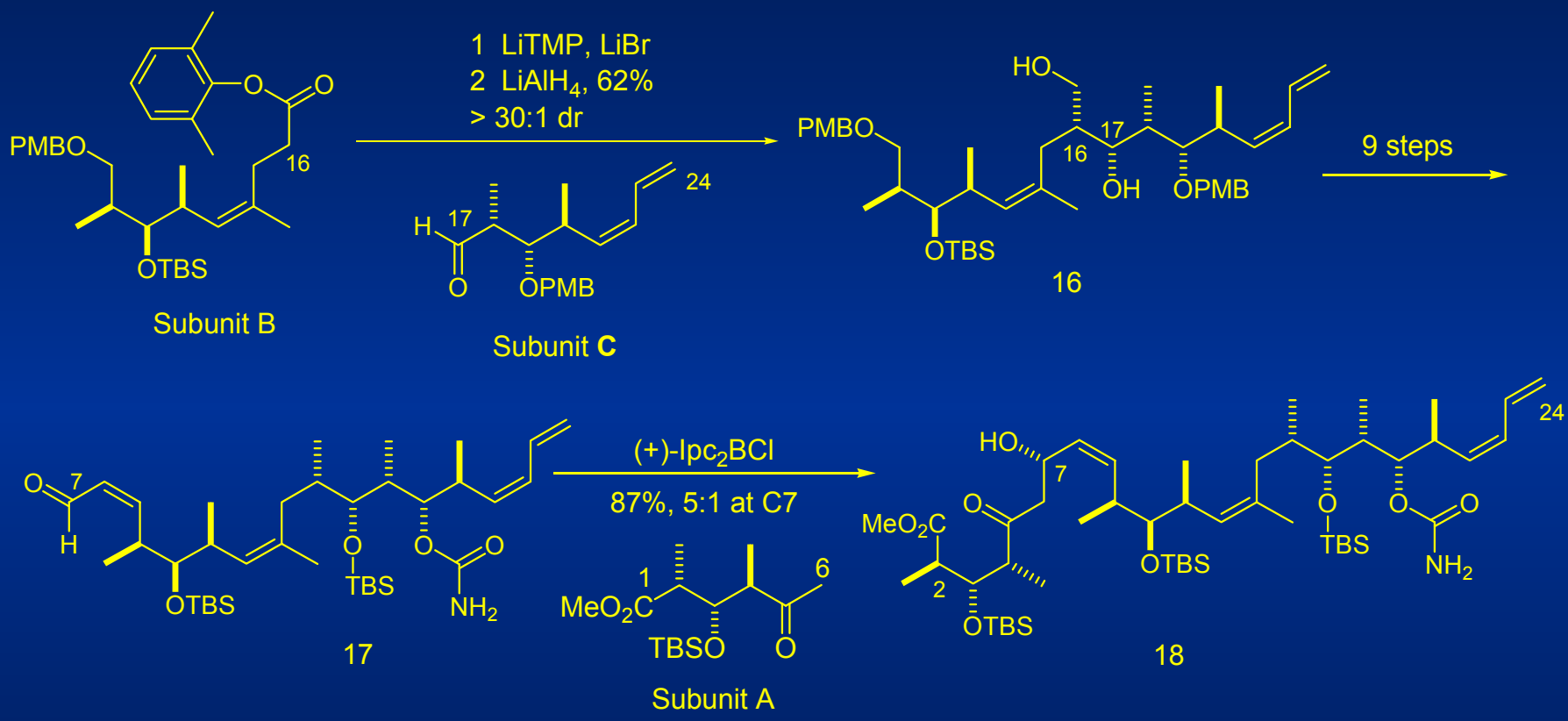


Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1985**, *26*, 5585.
Aicher, T. D.; Kishi, Y. *Tetrahedron Lett*. **1987**, *28*, 3463.

# Fragment coupling
# Smith



# Fragment coupling
# Paterson

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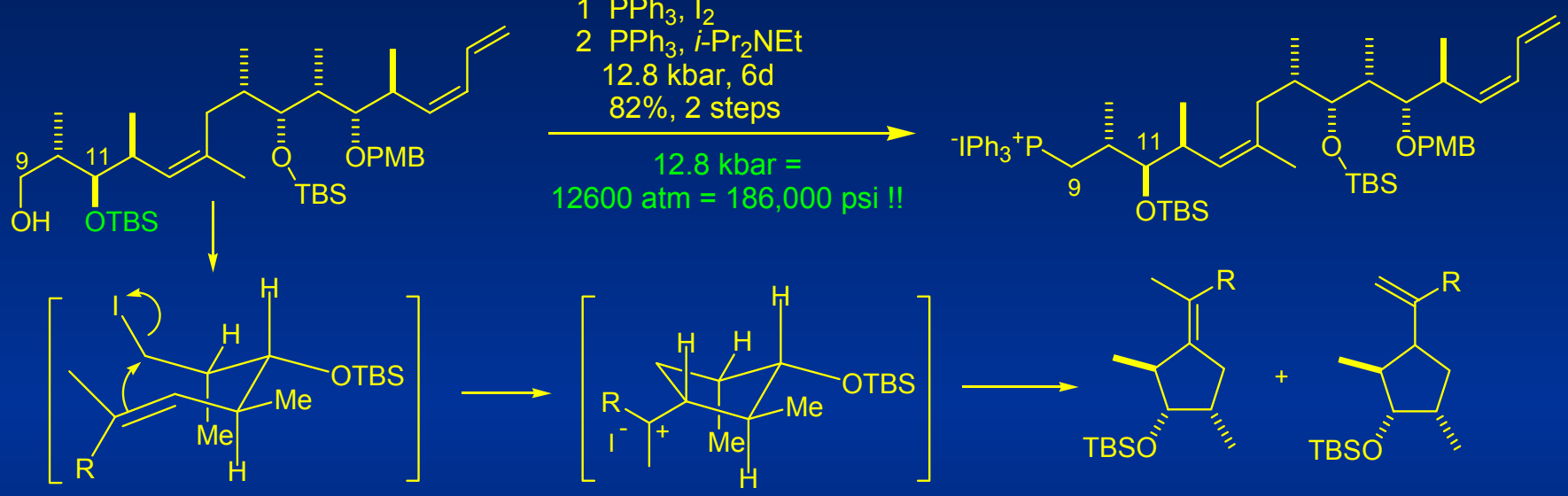
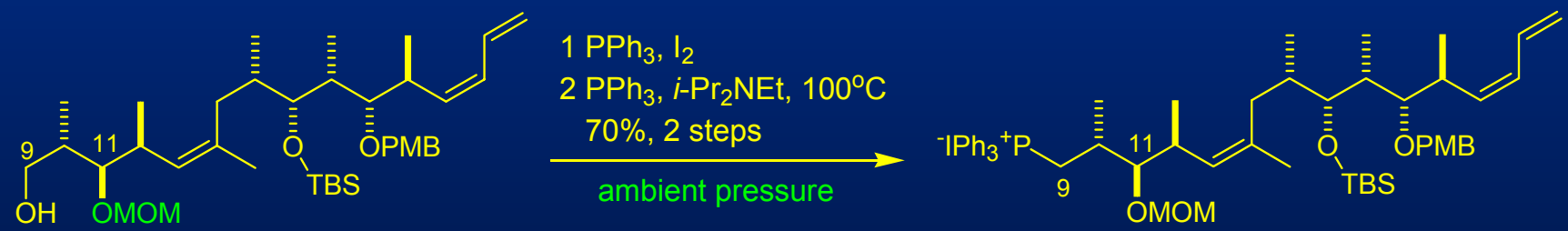
Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron*, **1990**, *46*, 4663.

Mulzer, J.; Berger, M. *J. Am Chem. Soc.* **1999**, *121*, 8393.

2nd Generation: ultrahigh pressure
Undesired intramolecular cyclization



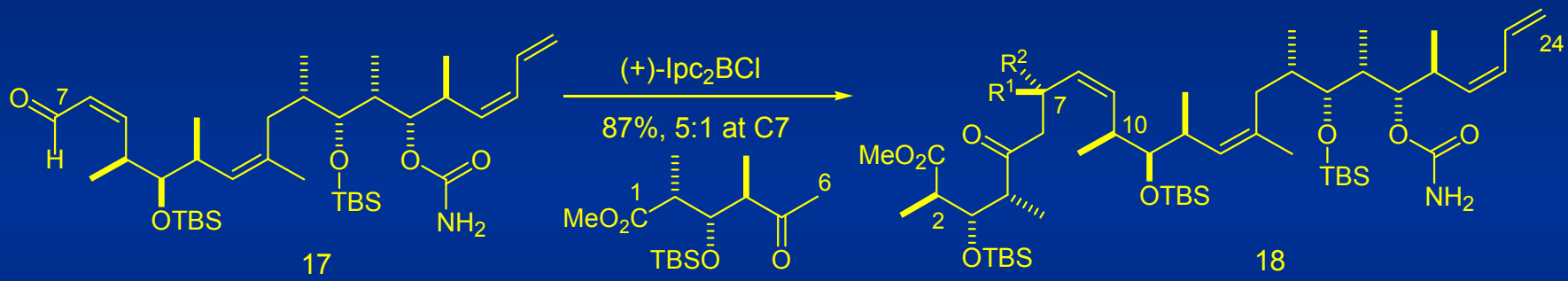

3rd Generation: improvement
Reduction of the steric bulk at C11

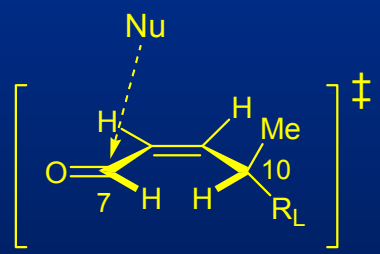



Smith, A.B. III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **2003**, *5*, 4405.

Paterson
1st generation

# Problem

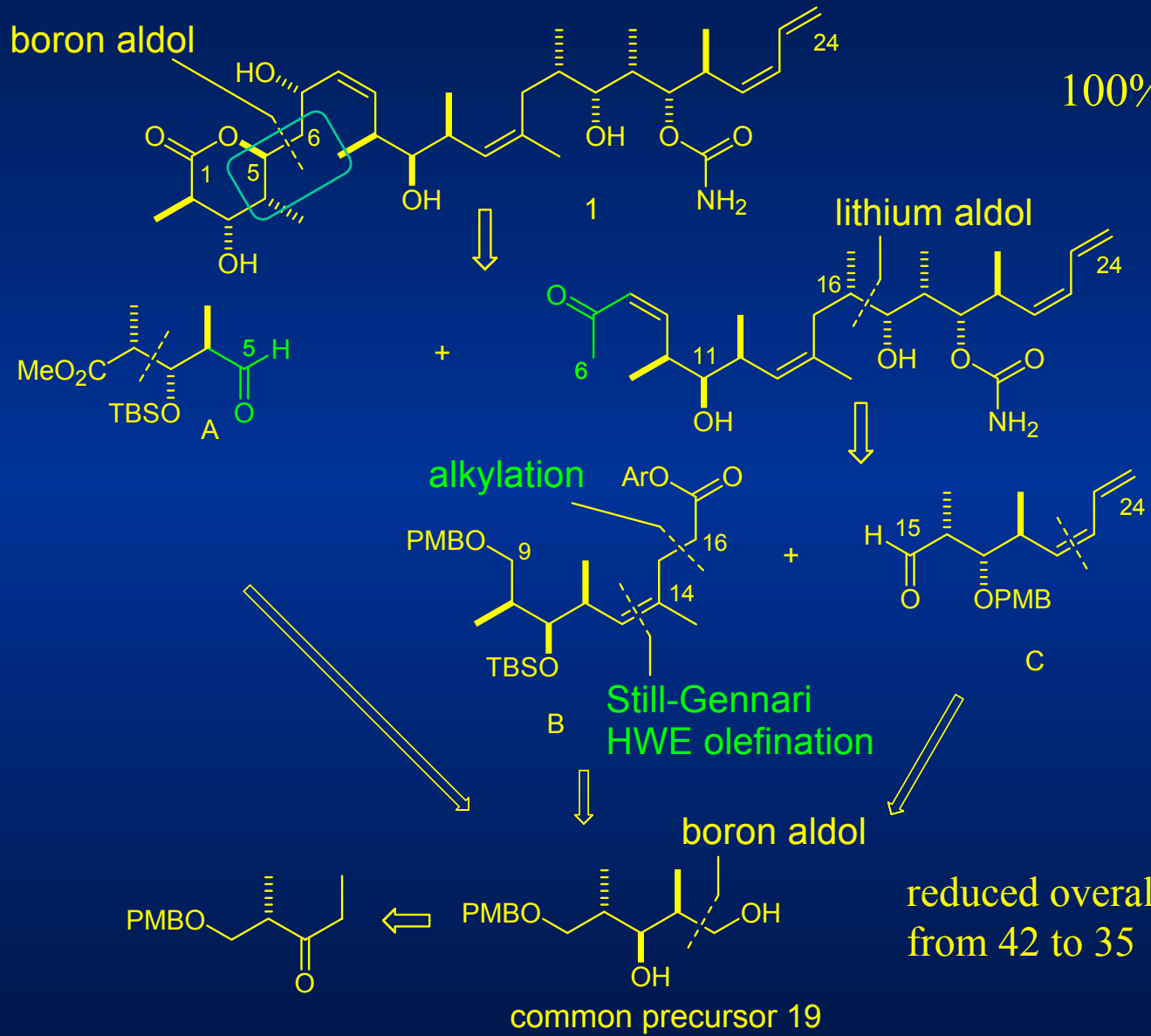



| reagent | 18a | : | 18b | yield |
|---|---|---|---|---|
| *c*-Hex$_2$BCl | 7 | : | 1 | 67% |
| (+)-Ipc$_2$BCl | 1 | : | 5 | 87% |

18a: $R^1$ = OH, $R^2$ = H
18b: $R^1$ = H, $R^2$ = OH (desired)

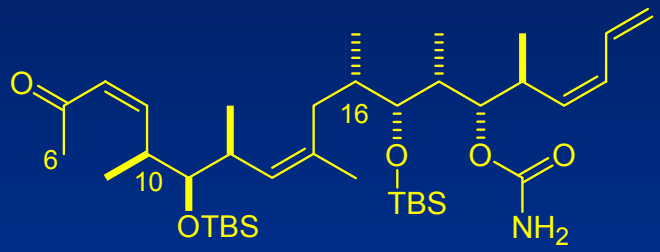
100% substrate control




reduced overall steps
from 42 to 35

Paterson
2nd Generation

# Improvement

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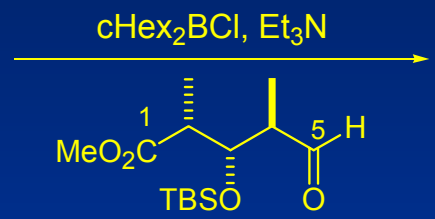
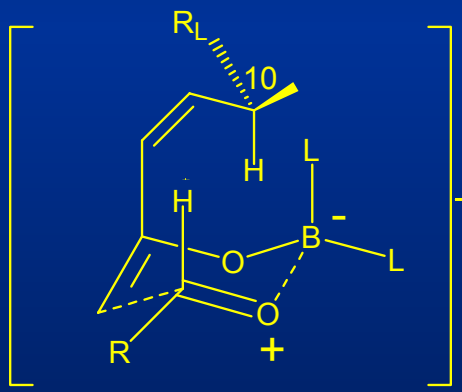
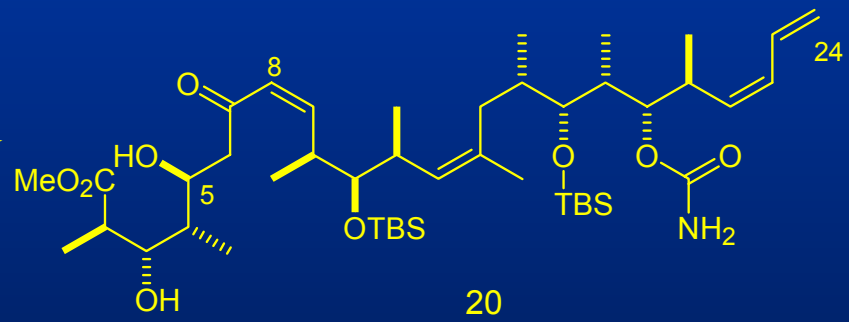



Subunit A



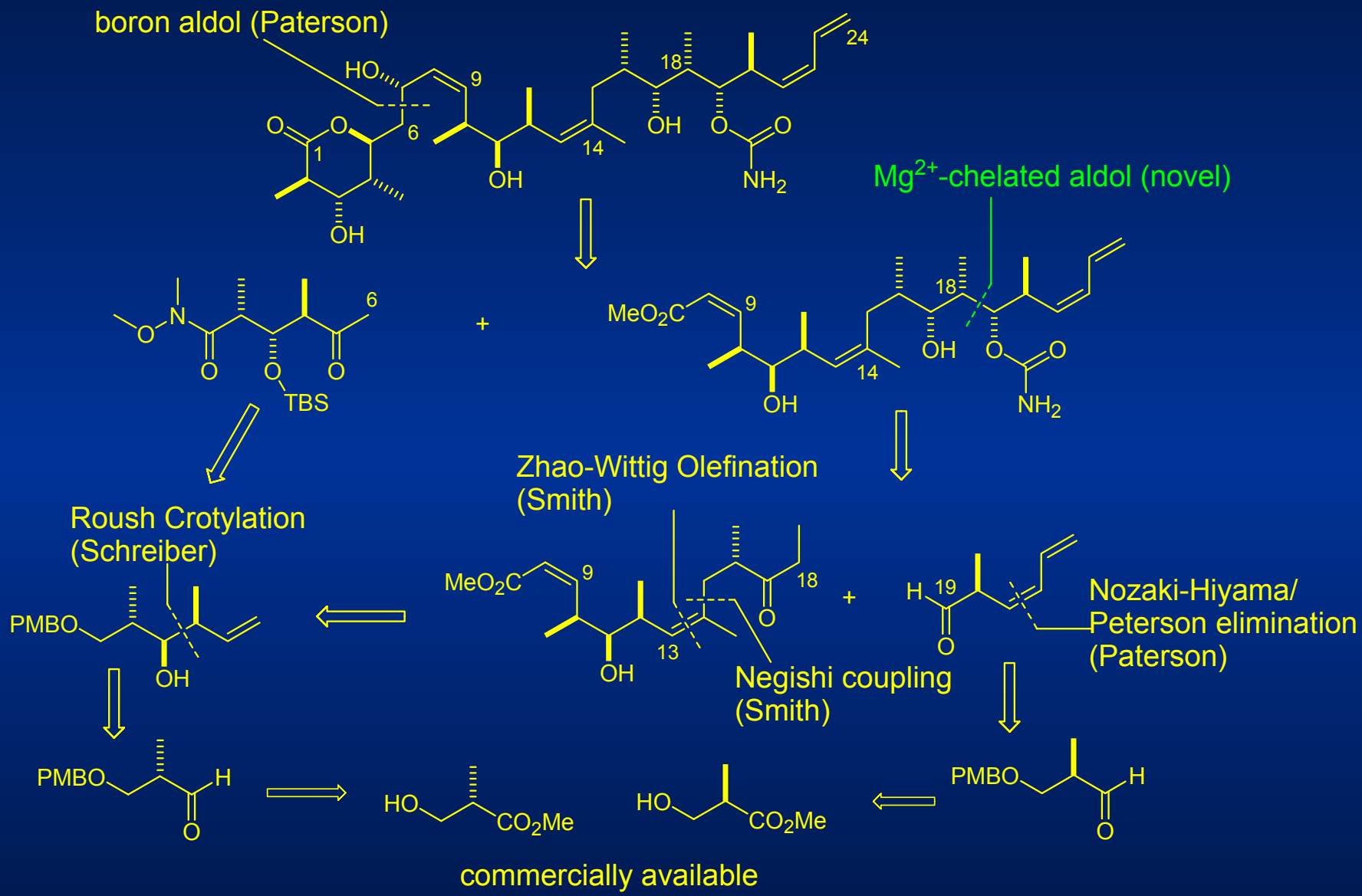

64%, 20:1 dr at C5




20

Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereinig, N. S. *Org. Lett.* **2003**, *5*, 35.

# Strategy by Novartis




Francavilla, C.; Chen, W.; Kinder, F. R. Jr. *Org. Lett.*, **2003**, *5*, 1233.

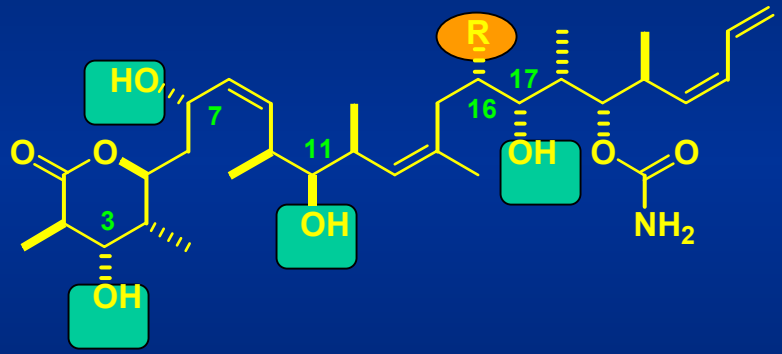
## Next Generation ???

| | Longest Linear Sequences | |
|---|---|---|
| | Steps | Yield |
| Schreiber | 24 | 4.3% |
| Smith | 24 | 6% |
| Myles | 25 | 1.4% |
| Marshall | 29 | 2.2% |
| Paterson | 23 | 10.3% |
| Novartis | 21 | N.A. |

Despite considerable synthetic efforts, there continues to be a pressing demand for a more practical and scaleable total synthesis …

# SAR Summary

Antiproliferative Potencies ($IC_{50}$, nM) Against A549 or MG63 Cells of Discodermolide (**1**), and Analogues **2-3e**.




| | A549 | MG63 |
|---|---|---|
| Discodermolide **1** (R = Me) | 3.6 | 6 |
| **2** (R = H; 16-demethyl) | n.d. | 10 |
| Acetylated analogues: | | |
| **3a** (3-OAc) | 3.8 | |
| **3b** (7-OAc) | 0.8 | |
| **3c** (3,7-OAc) | 0.8 | |
| **3d** (3,11-OAc) | 164 | |
| **3e** (3,17-OAc) | 524 | |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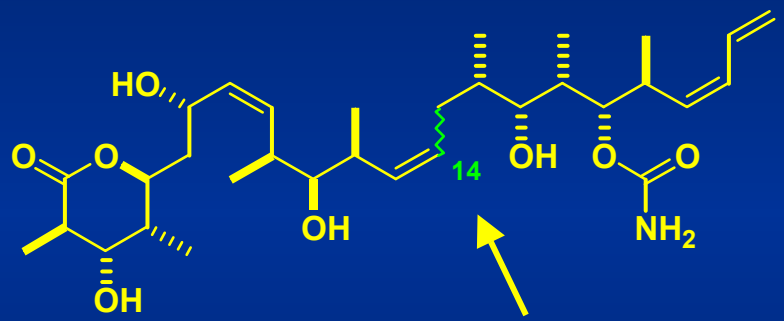
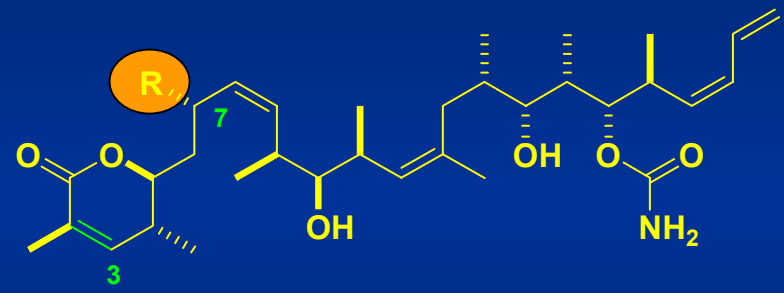
# SAR Summary

Antiproliferative Potencies ($IC_{50}$, nM) Against A549 Cells of Discodermolide (**1**), and Analogues **4a-4d**.




| | A549 |
|---|---|
| **4a** (14-*cis*, demethyl) | 7.8 |
| **4b** (14-*trans*, demethyl) | 485 |

| | A549 |
|---|---|
| **4c** (3-dehydro, R = OH) | 1.8 |
| **4d** (3-dehydro, R = H) | 11.4 |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# Summary

- Discodermolide, a marine natural product, shares the same microtubule-stabilizing mechanism as Taxol and has a promising anticancer profile.

- However, the supply problem is still hampering further biological and SAR studies. To date, total synthesis is the only economical means of providing useful quantities of Discodermolide. Despite considerable synthetic efforts, there continues to be a demand for a more practical and scaleable total synthesis.

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