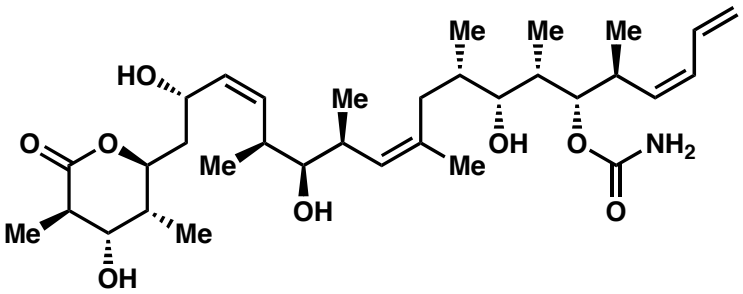
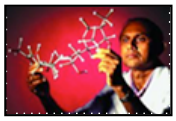
The Total Synthesis of Discodermolide



The Journey from 7 mg to 60 g



NOVARTIS

Literature Group Meeting
by Dan Caspi

Monday June 28, 2004 • 147 Noyes, 8 PM

Outline of Topics for Discodermolide

I. Introduction:

a. Structure and Bioactivity
b. Historical Outline

II. Smith Synthesis

a. First-Generation Route
b. Second-Generation Route
c. Third-Generation Route

III. Paterson Synthesis

a. First-Generation Route
b. Second-Generation Route

IV. Novartis Synthesis

a. Hybrid Smith-Paterson Approach

V. Conclusion

Partial Bibliography:

Gunasekera, S. P. *J. Org. Chem.* 1990, *55*, 4912-5.

(-) Schreiber, S. L. *J. Am. Chem. Soc.* 1993, *115*, 12621-2.
(-) Smith, A. B. *J. Am. Chem. Soc.* 1995, *117*, 12011-2.
(+) Schreiber, S. L. *J. Am. Chem. Soc.* 1996, *118,* 11054-80.
(-) Myles, D. C. *J. Org. Chem.* 1997, *62*, 6098-99.
(+) Marshall, J. A. *J. Org. Chem.* 1998, *63*, 7885-92.
(+) Smith, A. B. *Org. Lett.* 1999, *1*, 1823-6.
(+) Smith, A. B. *J. Am. Chem. Soc.* 2000, *122*, 8654-64.
(+) Paterson, I. *Angew. Chem. Int. Ed.* 2000, *39,* 377-80.
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(+) Kinder, F. R., Jr. *Org. Lett.* 2003, *5*, 1233-6. (Formal Total Synth.)
(+) Smith, A. B. *Org. Lett.* 2003, *5,* 4405-8.
(+) Myles, D. C. *J. Org. Chem.* 2003, *68*, 6646-60.
(+) Paterson, I. *Org. Lett.* 2003, *5*, 35-8.

(+) Mickel, S. J. *Org. Proc. Res. Dev.* 2004, *8,* 92-130 (5 papers).
(+) Loiseleur, O. *Org. Proc. Res. Dev.* 2004, *ASAP*.

Reviews:

Chemtracts 2000, *13*, 229-36.
Paterson, I. *Eur. J. Org. Chem.* 2003, 2193-2208.
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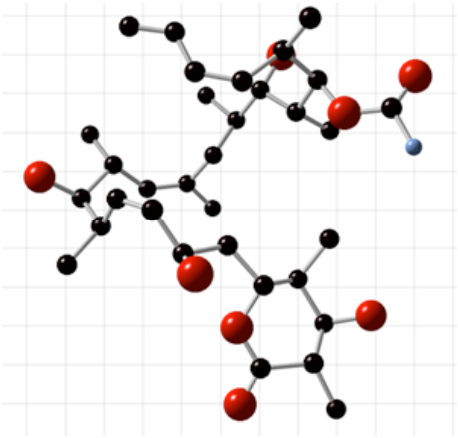
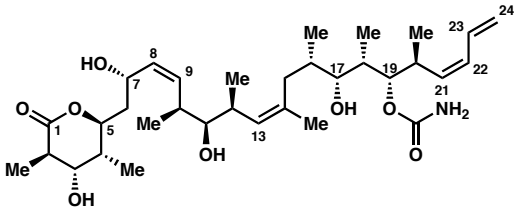
The Structure of Discodermolide

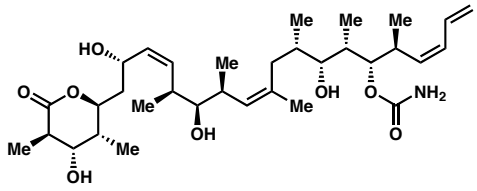


(Hydrogens omitted for clarity)

- Structure determined by extensive spectroscopic studies as well as single-crystal X-ray.
- Linear polypropionate chain containing 13 stereocenters, 6 of which bear hydroxyls, remaining 7 bear methyls.
- Contains a tetrasubstituted δ-lactone, two di- and one trisubstituted (Z)-alkene.
- Contains a carbamate moiety and a terminal (Z)-diene.
- Discodermolide adopts a U-shaped conformation, where the internal (Z)-alkenes act as conformational locks by minimizing A(1,3) strain and *syn*-pentane interactions along the backbone.
- The δ-lactone is held in a boat-like conformation.



Why is Total Synthesis of Discodermolide Important?



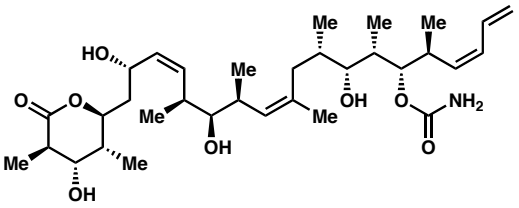
Bioactivity:

- Initial studies revealed that (+)-discodermolide was an apparent immunosuppresant.
- Later studies revealed that Discodermolide stabilizes microtubes faster and more potently than any of the other known MTS agents, and is a potent inhibitor of tumor cell growth in vitro including Taxol-resistant cells. It is also more water soluble than Taxol.
- Promising synergy observed when used in combination with Taxol.
- Licensed by Novartis in 1998 to develop it as a new-generation anticancer drug. Currently, in Phase I Clinical Trials.

Production:

- From deep-water marine sponge, *Discodermia dissoluta*, which must be harvested by manned submersibles off the Bahamas at a depth in excess of 33 m.
- Natural material is scarce: 0.002% w/w from frozen sponge (7 mg isolated from 454 g of crude)
- Fermentation has not been succesful to date.

Discodermolide "Highlights" Timeline



Harbor Branch Oceanographic Institution, Inc., FL
Led by S. Guanasekera. Isolation Paper.

J. Org. Chem. **1990**, *55*, 4912-5.
Correction: *J. Org. Chem.* **1991**, *56*, 1346.

S. Schreiber. *Chem. Biol.* **1994.**
First Natural Enantiomer Synthesis.

A. B. Smith. Gram-Scale Synthesis.

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1990 | 1995 | 2000 | 2005

S. Schreiber. First Total Synthesis.

J. Am. Chem. Soc. **1993**.

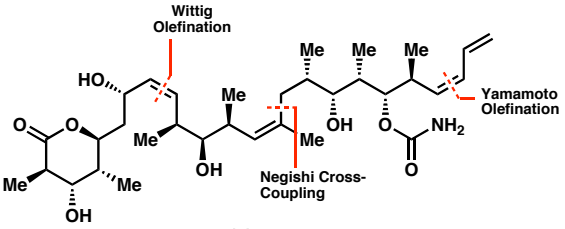
Licensed by Novartis.

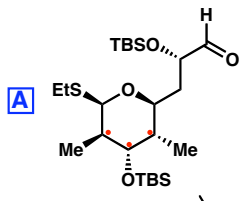
S. Mickel. Novartis Process Group.

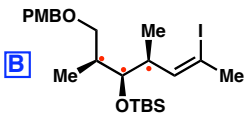
Org. Res. Proc. Dev. **2004**.

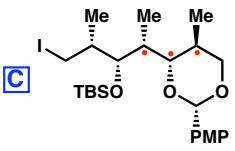
Amos B. Smith, III: First Generation Approach

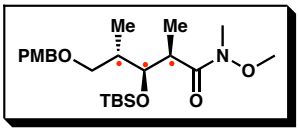
The absolute stereochemistry was unknown when they began the synthesis.









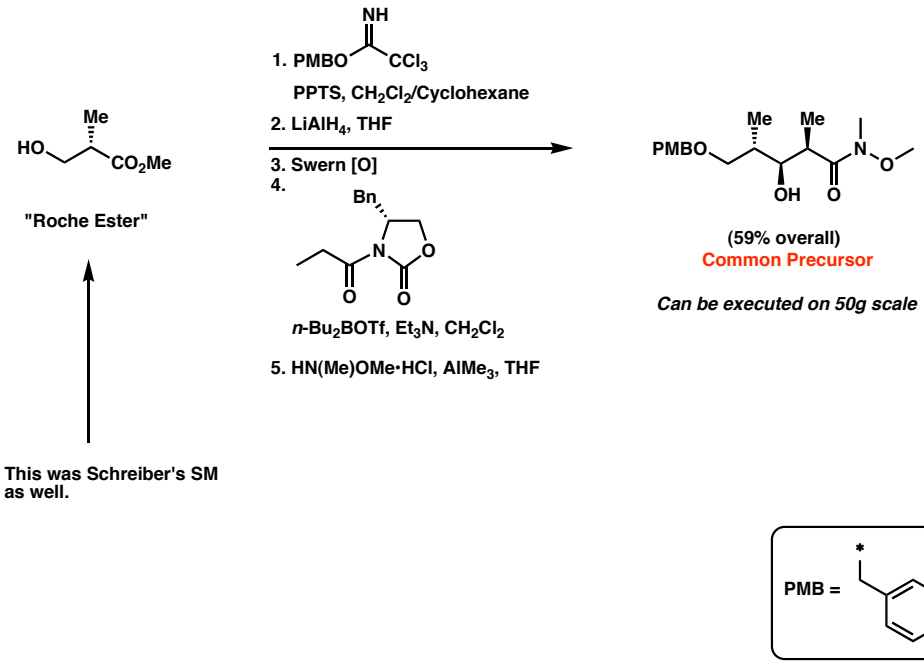


Can these fragments be derived from a common precursor?

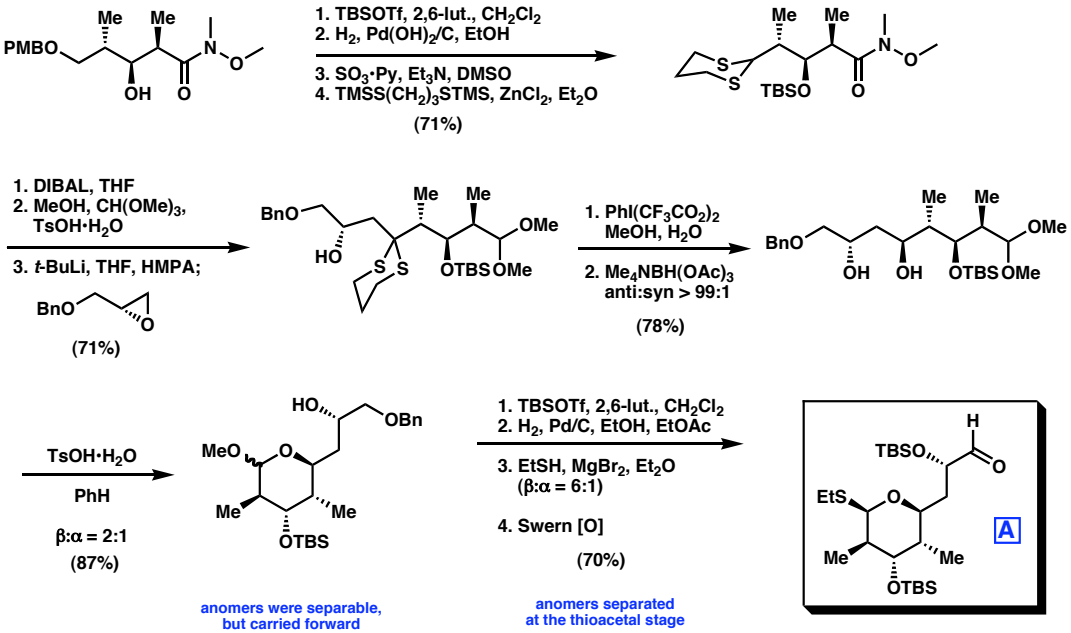
• Denotes the repeating stereochemical triad.

J. Am. Chem. Soc. **1995**, *117*, 12011-2.

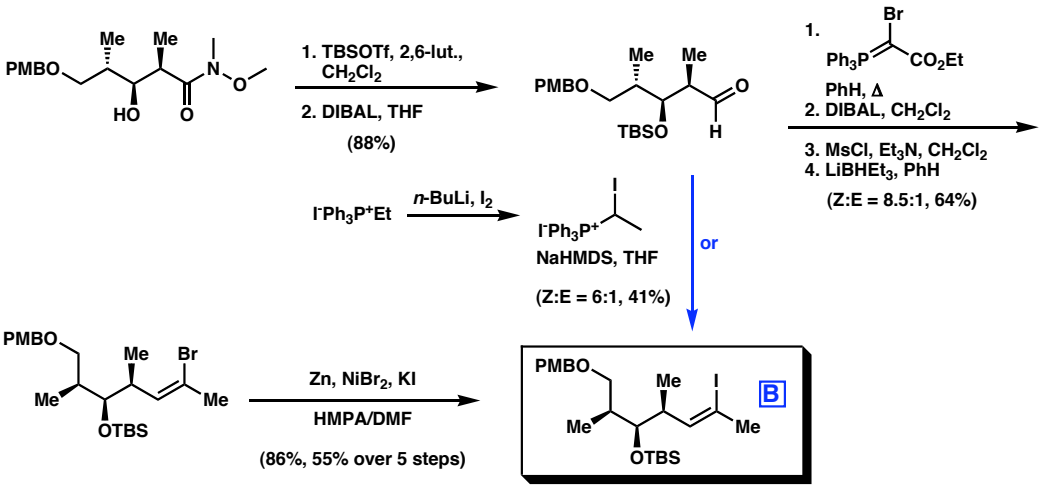
Amos B. Smith, III: Constructing the Common Precursor



Amos B. Smith, III: Constructing Fragment A

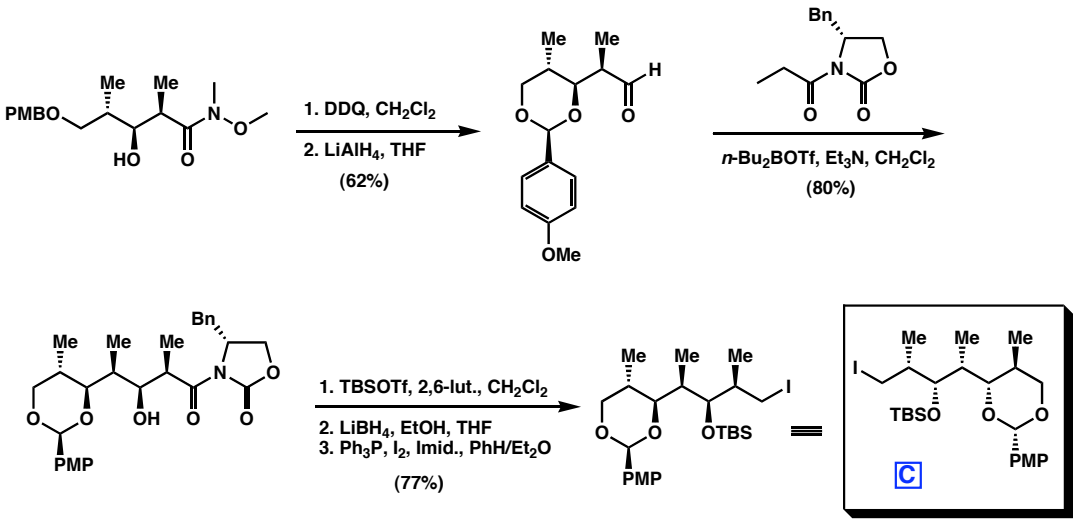


Amos B. Smith, III: Constructing Fragment B

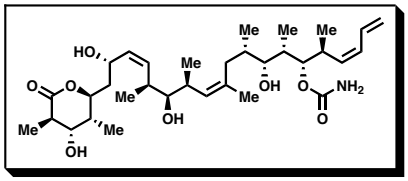


olefin geometry checked by halogen-metal exchange, only *t*-BuLi in Et_2O completely prevented a retro-[1,5]-Brook rearrangement.

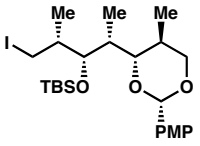
Amos B. Smith, III: Constructing Fragment C



Amos B. Smith, III: Fragment Coupling B and C



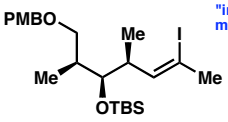
postulated that a mixed *t*-butyl-alkyl zinc intermediate is reactive in the process



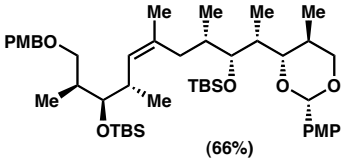
+ $ZnCl_2$ (premixed)

t-BuLi (3 eq.), Et_2O, -78 °C

then $Pd(PPh_3)_4$, Et_2O, rt

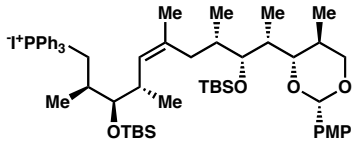


"intimate mixture"



(66%)

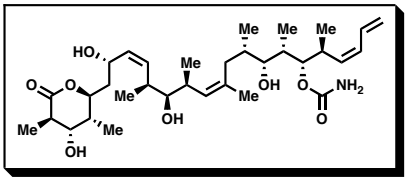
1. DDQ (1.05 eq.) CH_2Cl_2/H_2O
2. PPh_3, I_2, Imid. PhH/Et_2O
3. PPh_3 (15 eq.), *i*-PrNEt (3 eq.) 80 °C neat

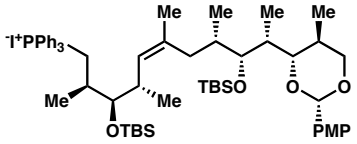


(87% for DDQ, 37% for next 2 steps)

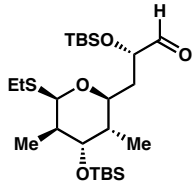
problems with competing cyclization, esp. with more polar solvent

Amos B. Smith, III: Fragment Coupling BC and A

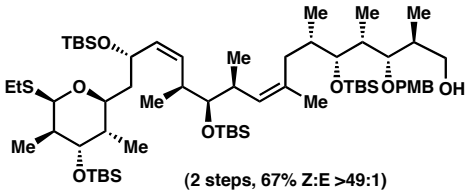




1. NaHMDS, THF



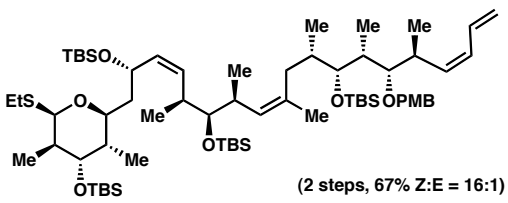
2. DIBAL, CH_2Cl_2



(2 steps, 67% Z:E >49:1)

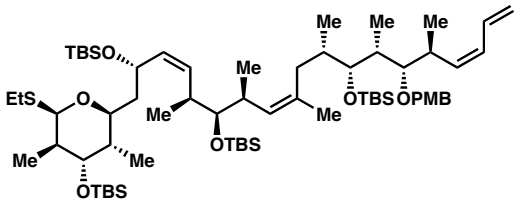
1. SO_3·Py, Et_3N, DMSO, CH_2Cl_2
2. $Ph_2PCH_2CH{=}CH_2$, *t*-BuLi, $Ti(O\textit{i}\text{-}Pr)_4$, MeI, THF

Yamamoto Olefination



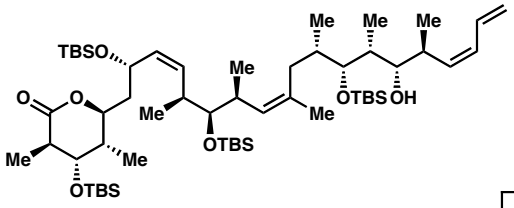
(2 steps, 67% Z:E = 16:1)

Amos B. Smith, III: Completion (First Generation)



1. $HgCl_2$, MeCN, THF; pH 7 buffer
2. DMSO, Ac_2O
3. DDQ, CH_2Cl_2, H_2O

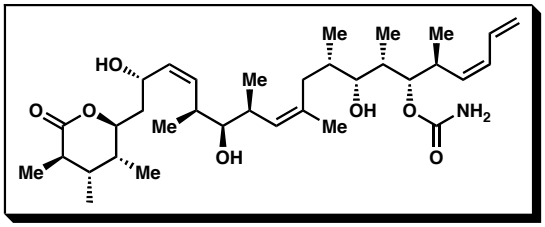
(66%)



Kokovsky Protocol

1. $Cl_3CCONCO$, DCE
   K_2CO_3, MeOH
2. 48% HF/MeCN (1:9)

(53%)



(–)-Discodermolide

(note: opposite enatiomer pictured)

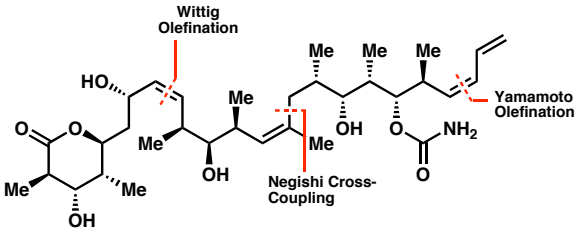
Amos B. Smith, III: Second Generation Approach

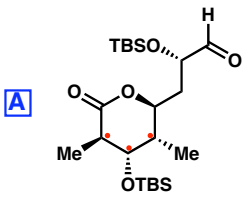
New Goals:

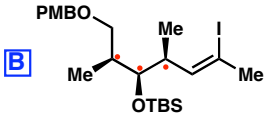
- Prepare 1 g of Discodermolide
- Use Similar Strategy

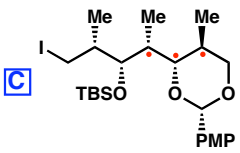
Problems from G1 Synthesis:

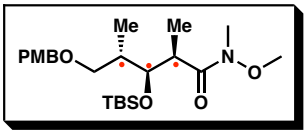
- Long Synthesis of A
- Poor Yield on Phosphonium Salt







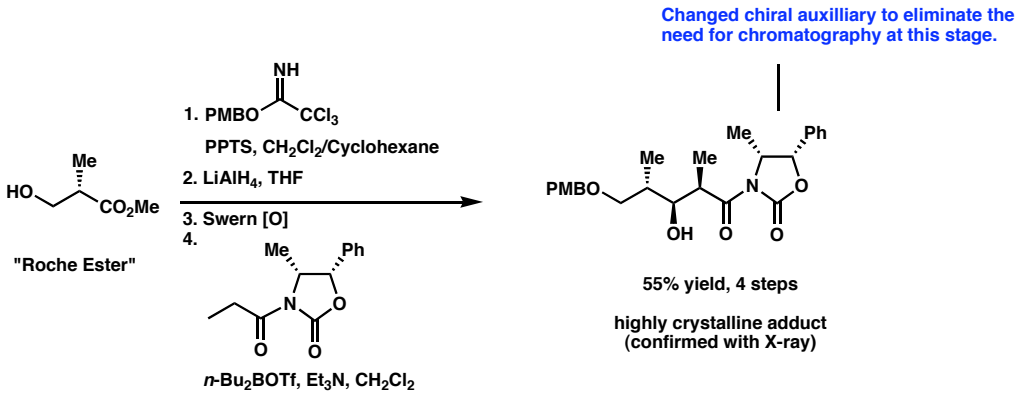


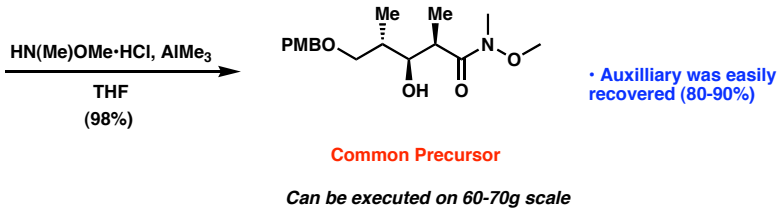


• Denotes the repeating stereochemical triad.

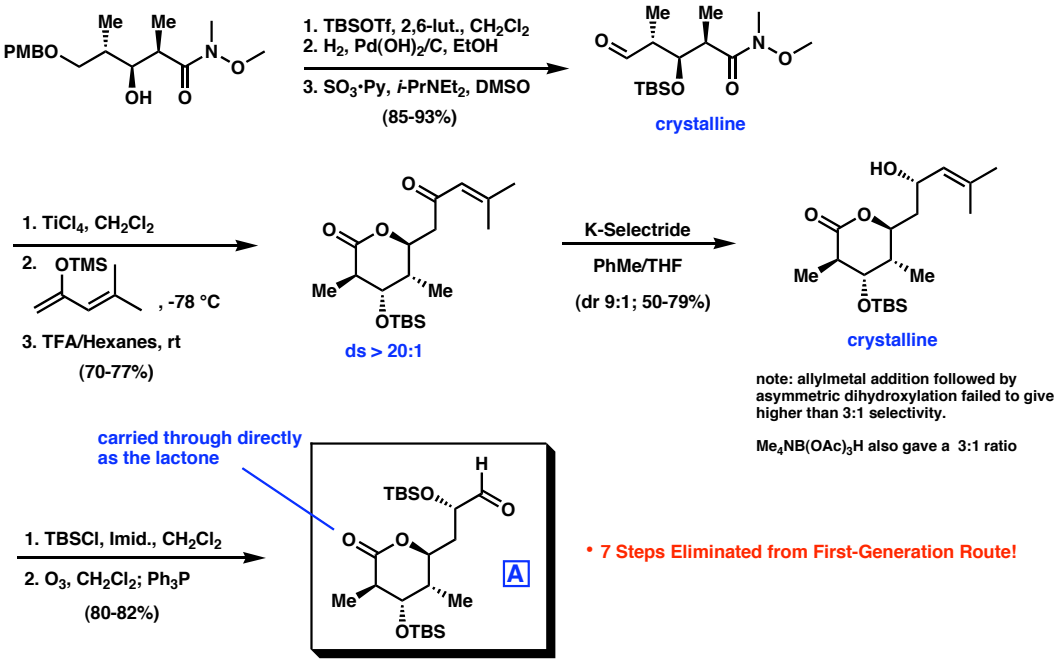
Org. Lett. **1999**, *1*, 1823-6.

Amos B. Smith, III: Constructing the Common Precursor

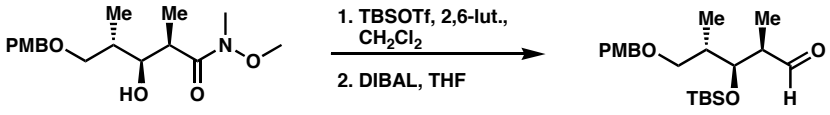


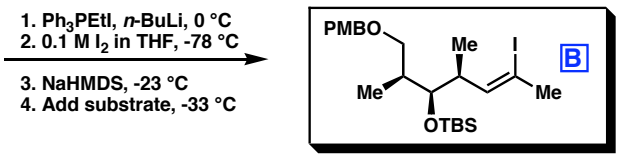


Amos B. Smith, III: Constructing Fragment A



Amos B. Smith, III: Constructing Fragment B

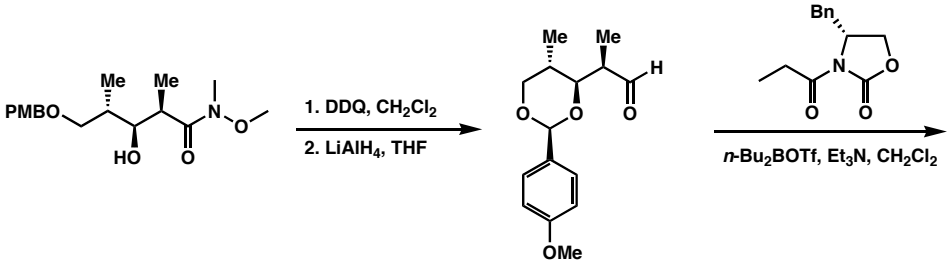


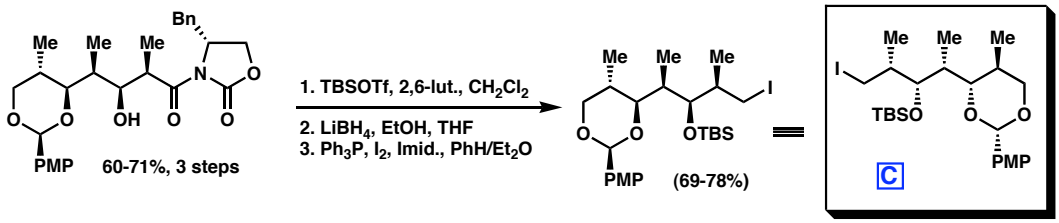


• Single Chromatography Required

(40-46% overall, ds 8-17:1)

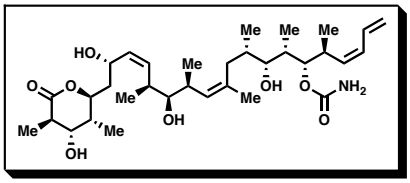
Amos B. Smith, III: Constructing Fragment C

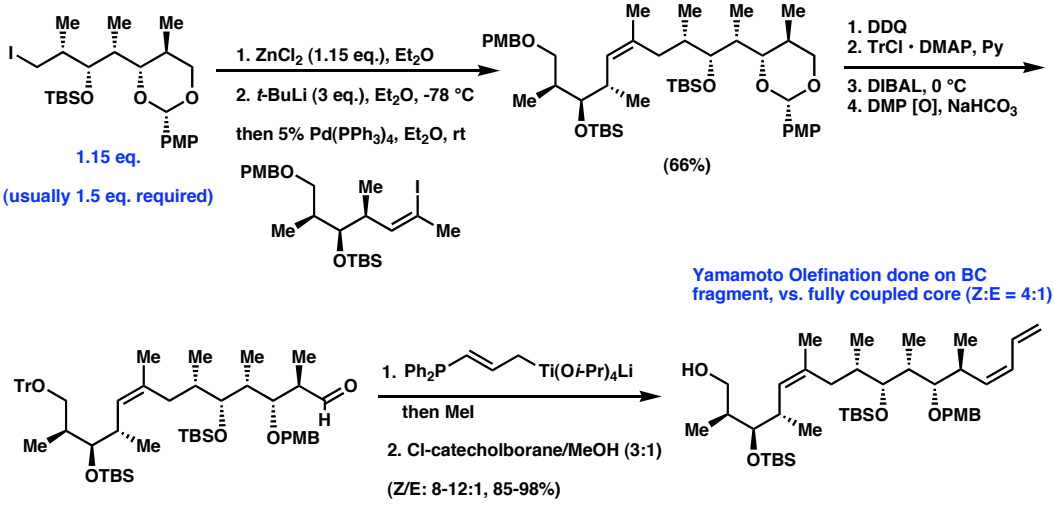




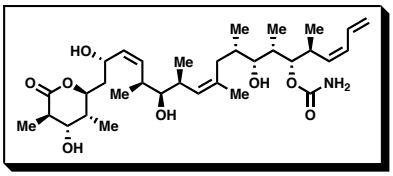
No Major Changes Here...

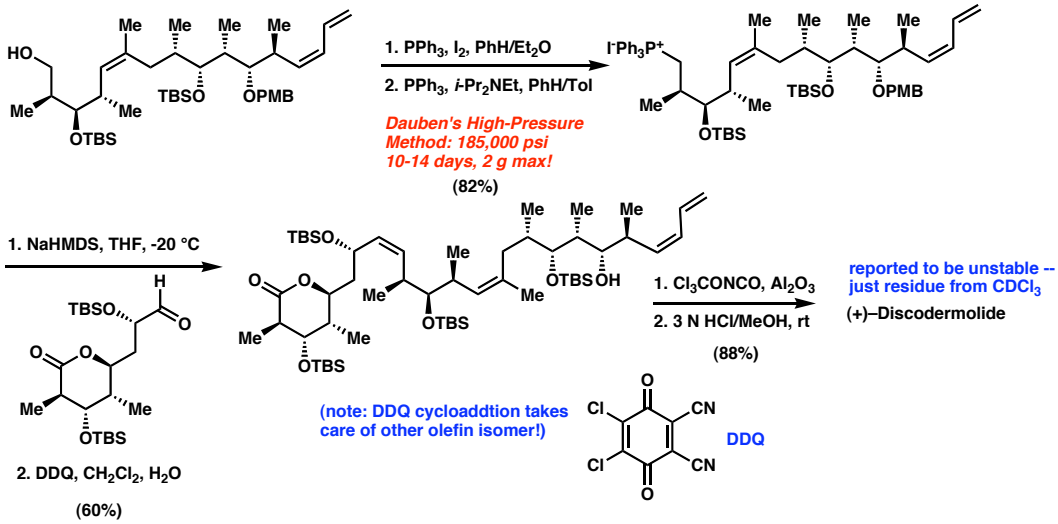
Amos B. Smith, III: Fragment Coupling B and C



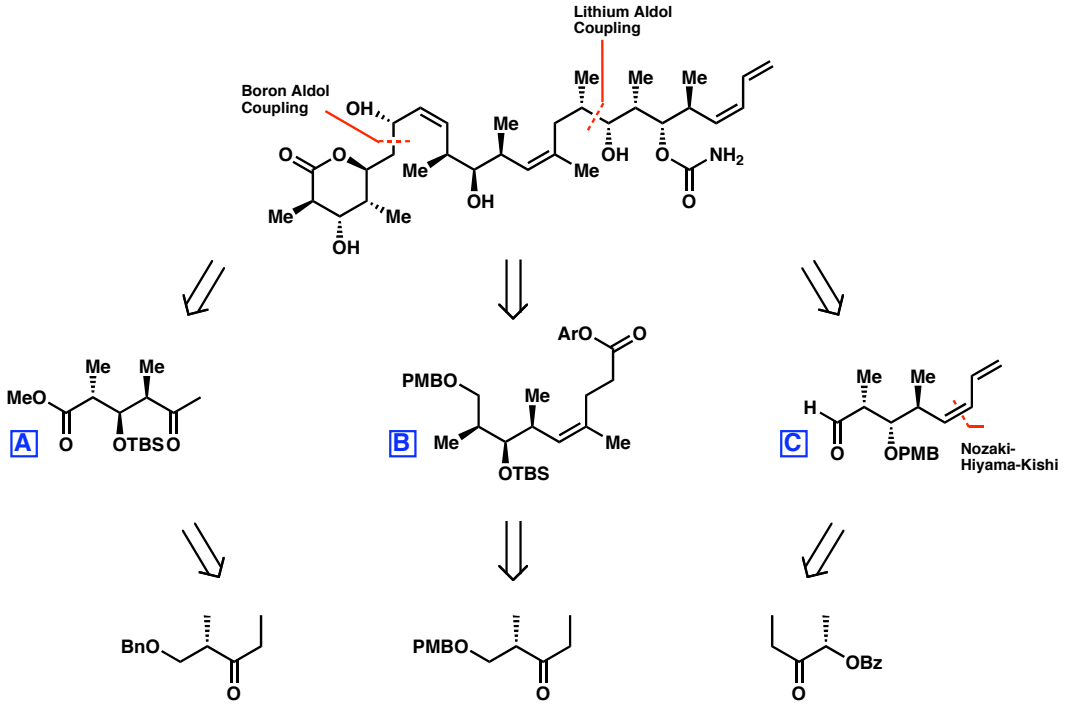


Amos B. Smith, III: Fragment Coupling BC and A



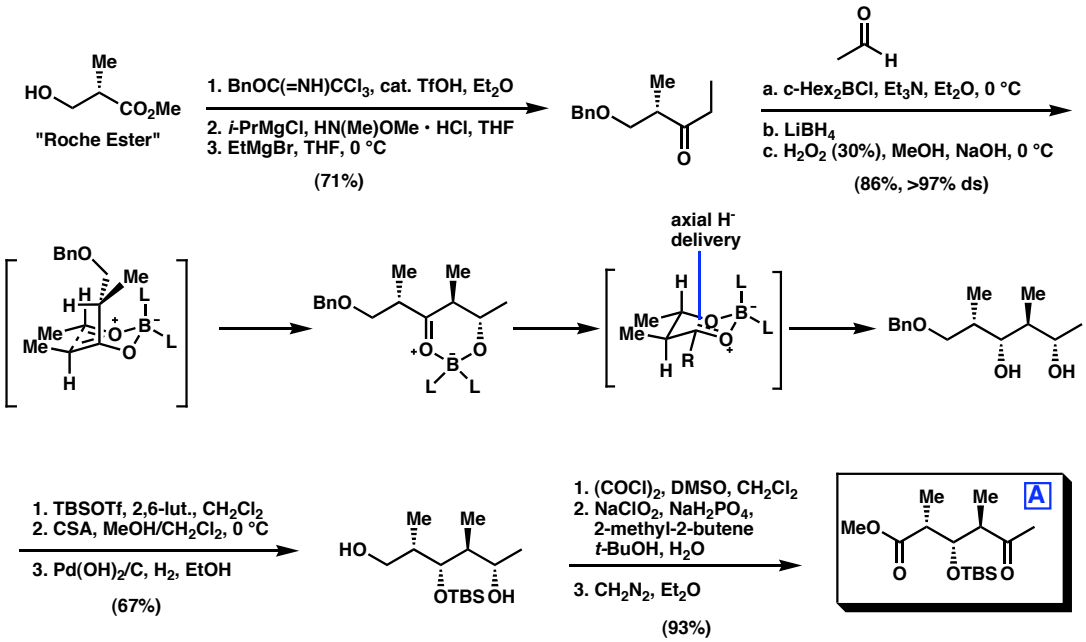


Ian Paterson: Retrosynthetic Analysis

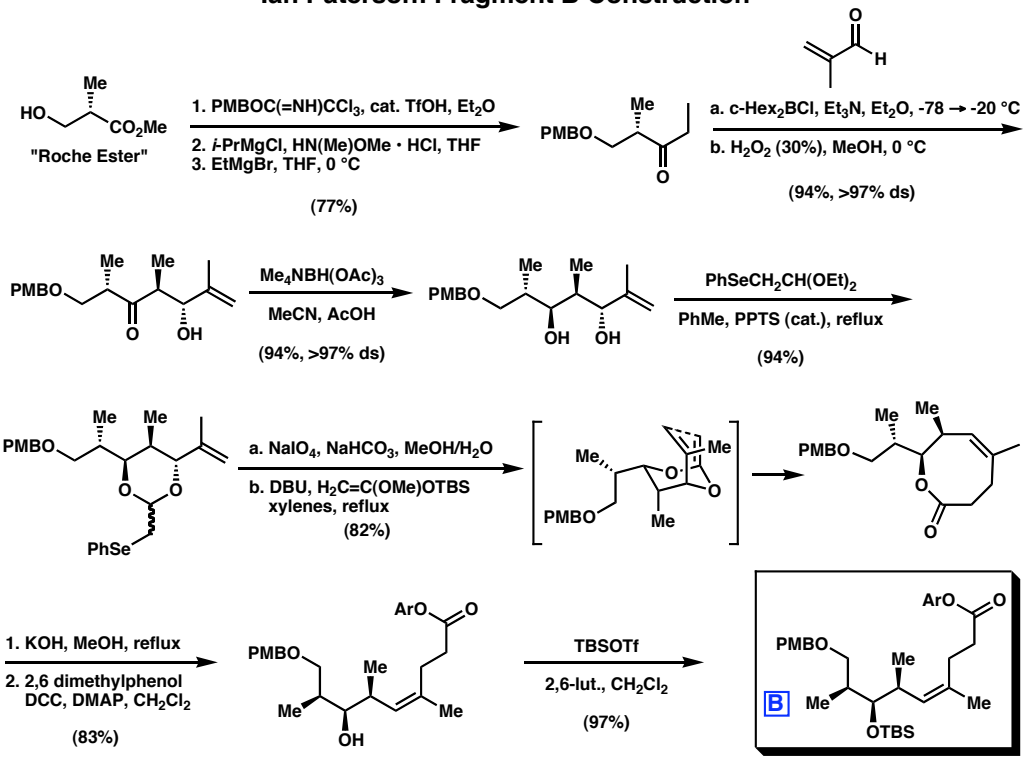


Angew. Chem. Int. Ed.. **2000**, *39*, 377-80.

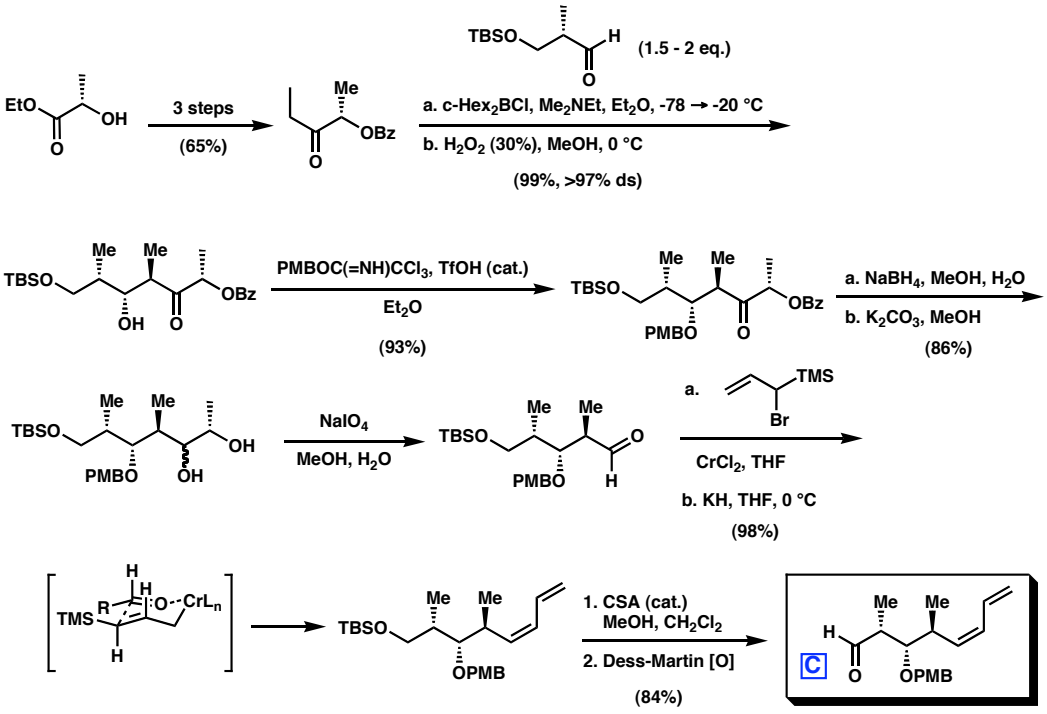
Ian Paterson: Fragment A Construction



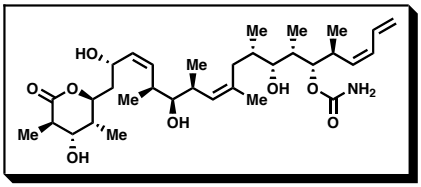
Ian Paterson: Fragment B Construction

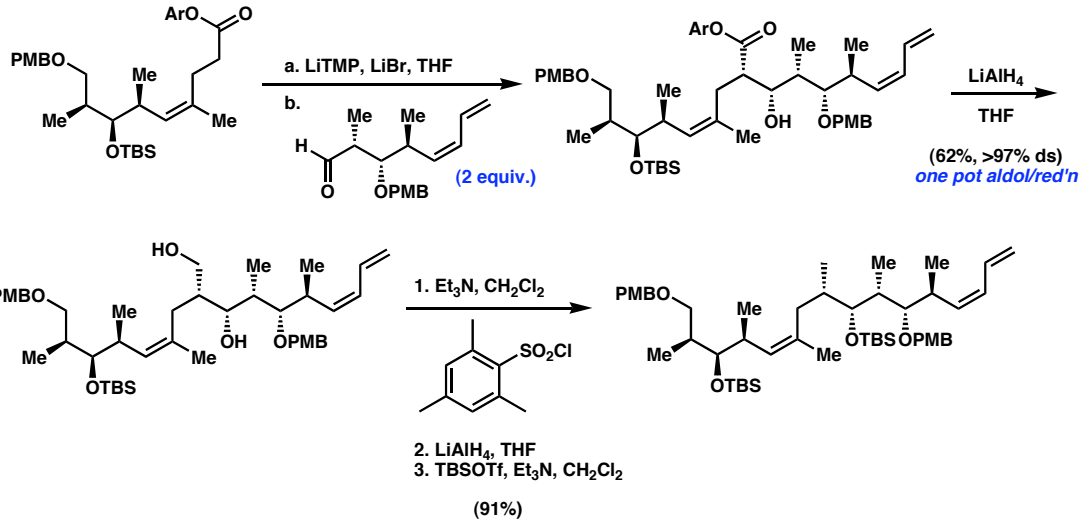


Ian Paterson: Fragment C Construction

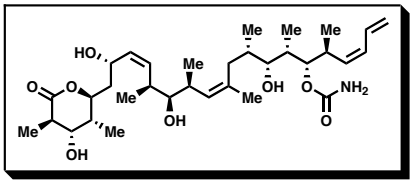


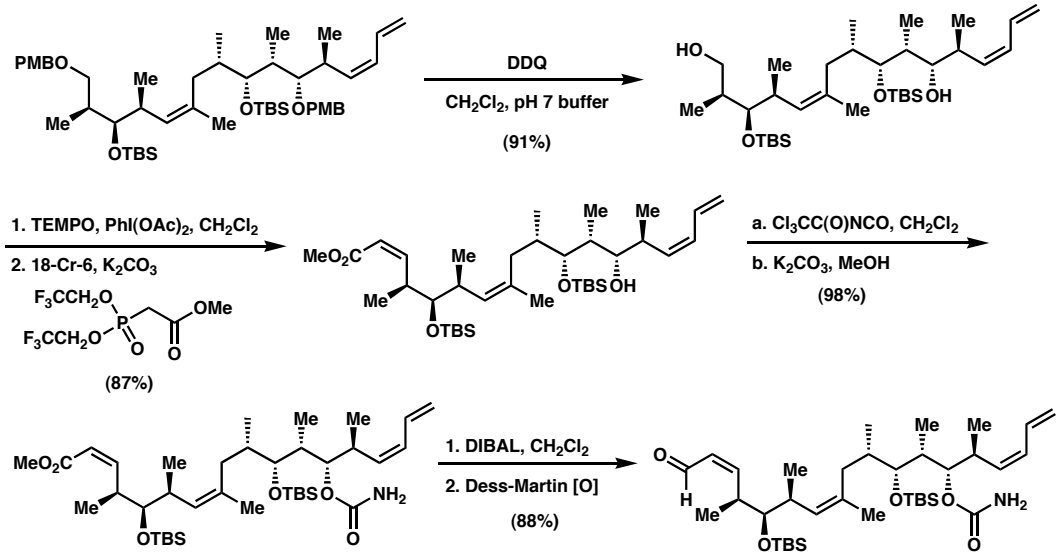
Ian Paterson: Coupling B and C



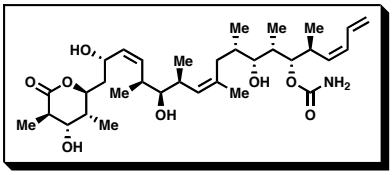


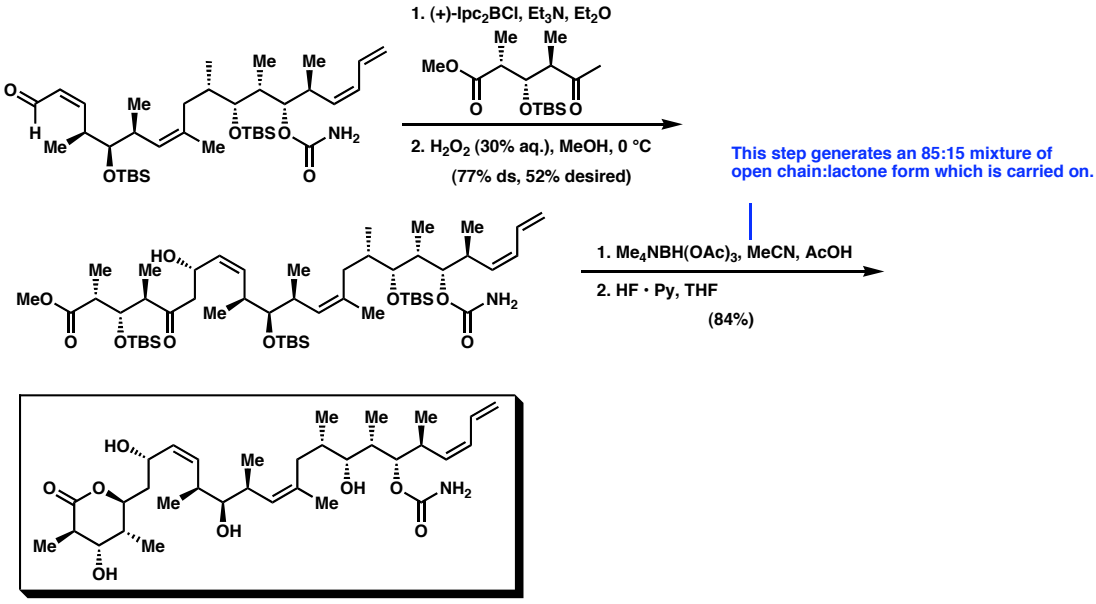
Ian Paterson: Elaboration of the BC fragment





Ian Paterson: Completion of the Synthesis

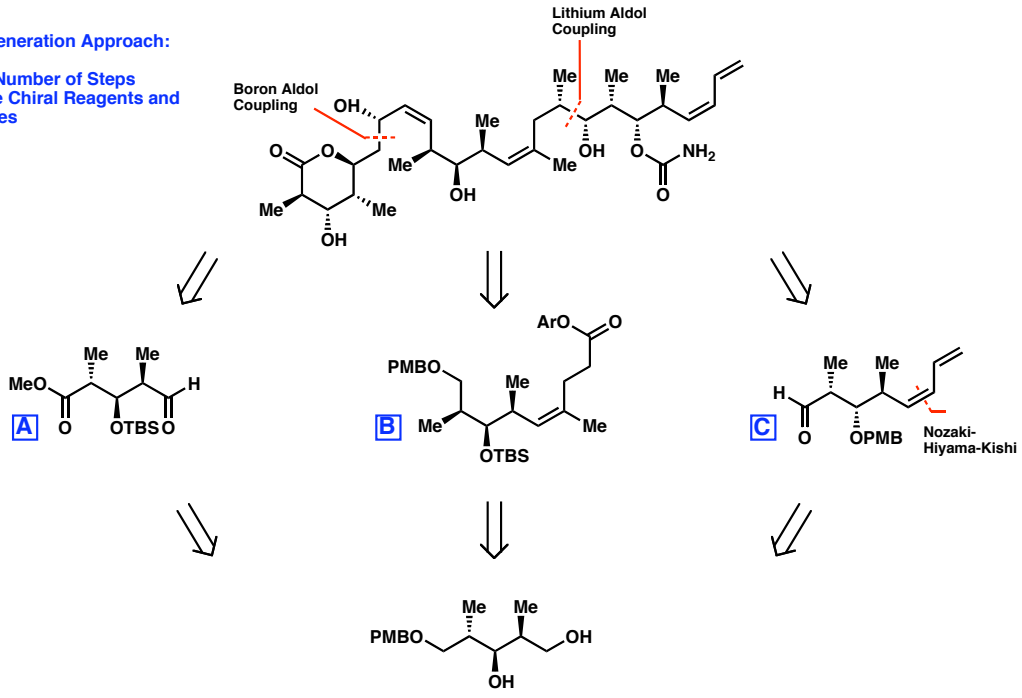




Ian Paterson: Second Generation Retrosynthesis

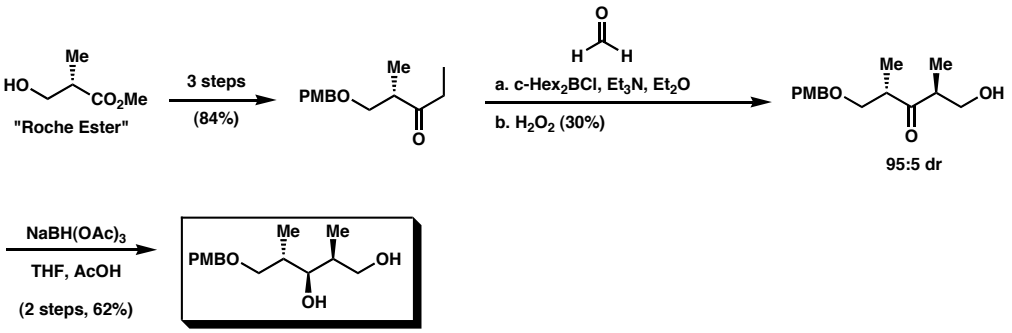
Second Generation Approach:

- **Reduce Number of Steps**
- **Eliminate Chiral Reagents and Auxillaries**

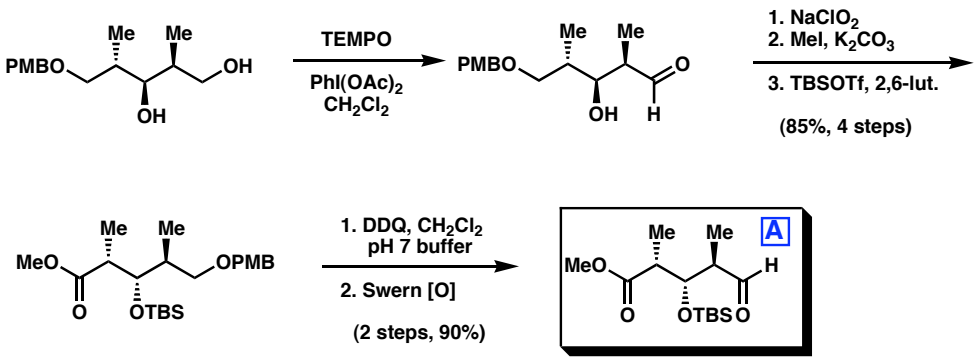


Org. Lett. **2003**, *5*, 35-8.

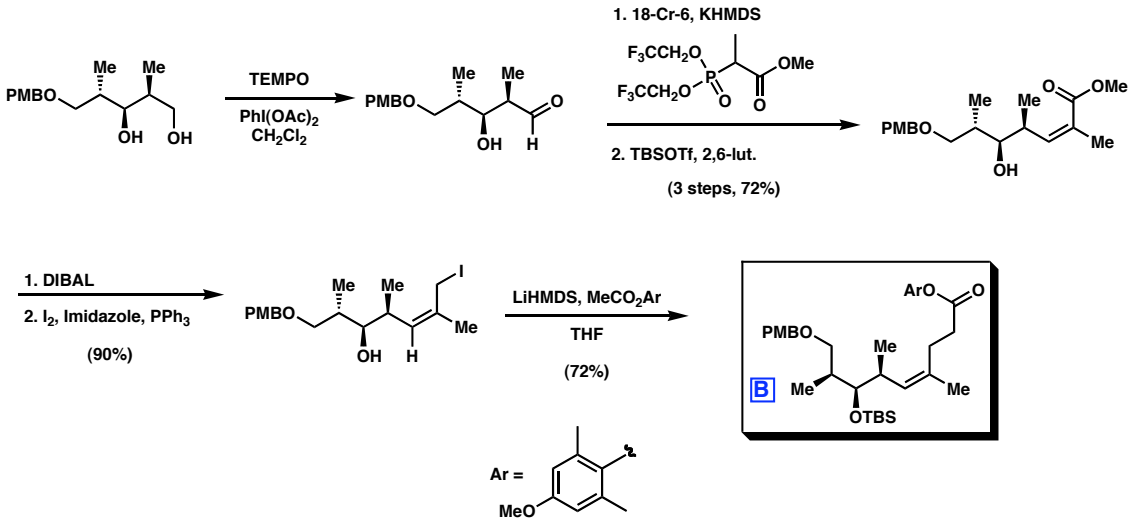
Ian Paterson: Common Precursor



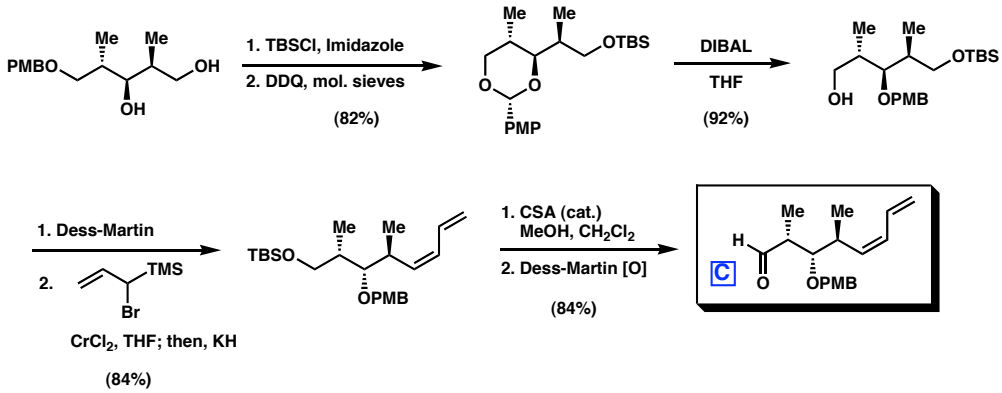
Ian Paterson: Fragment A Construction



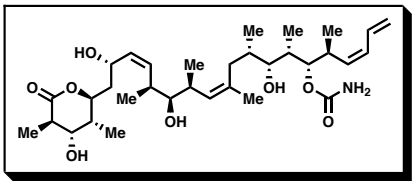
Ian Paterson: Fragment B Construction

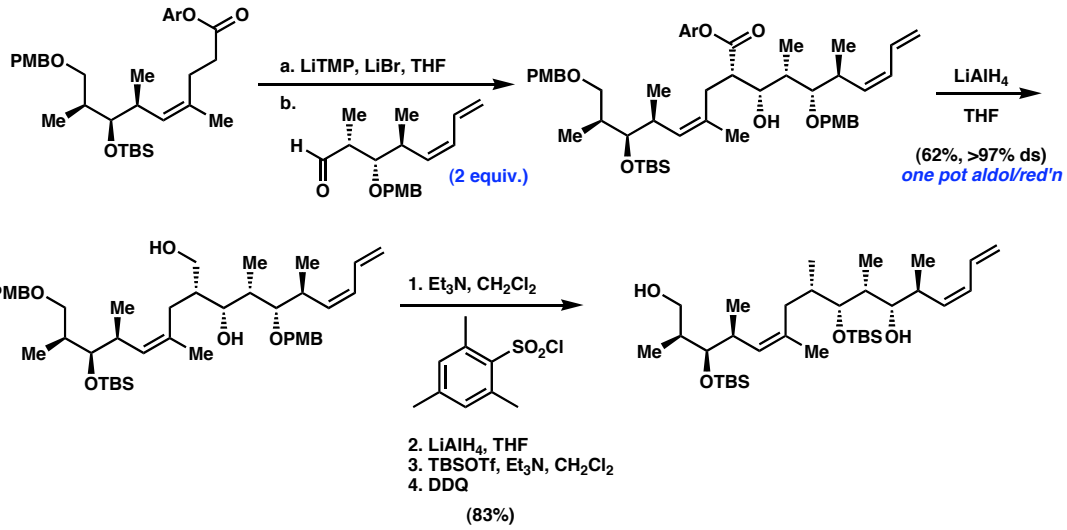


Ian Paterson: Fragment C Construction

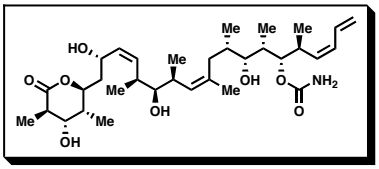


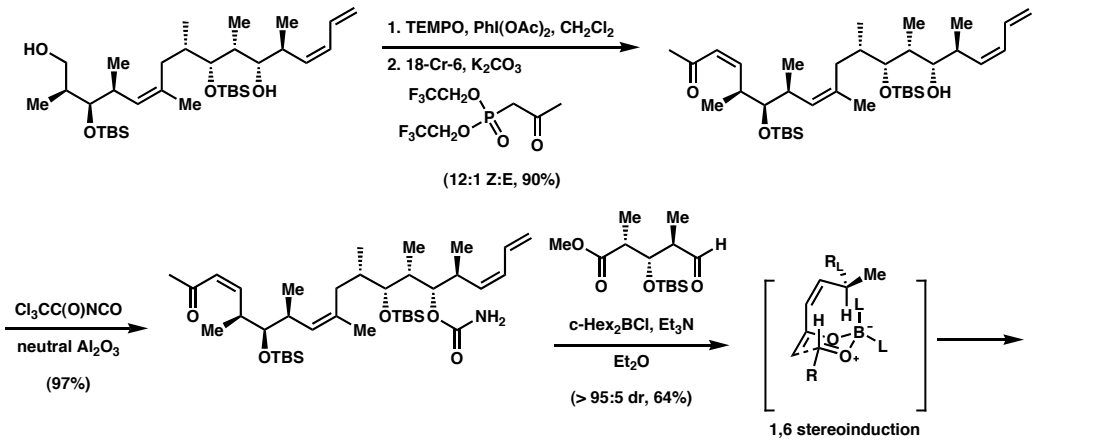
Ian Paterson: Coupling B and C





Ian Paterson: Endgame (2nd Generation)



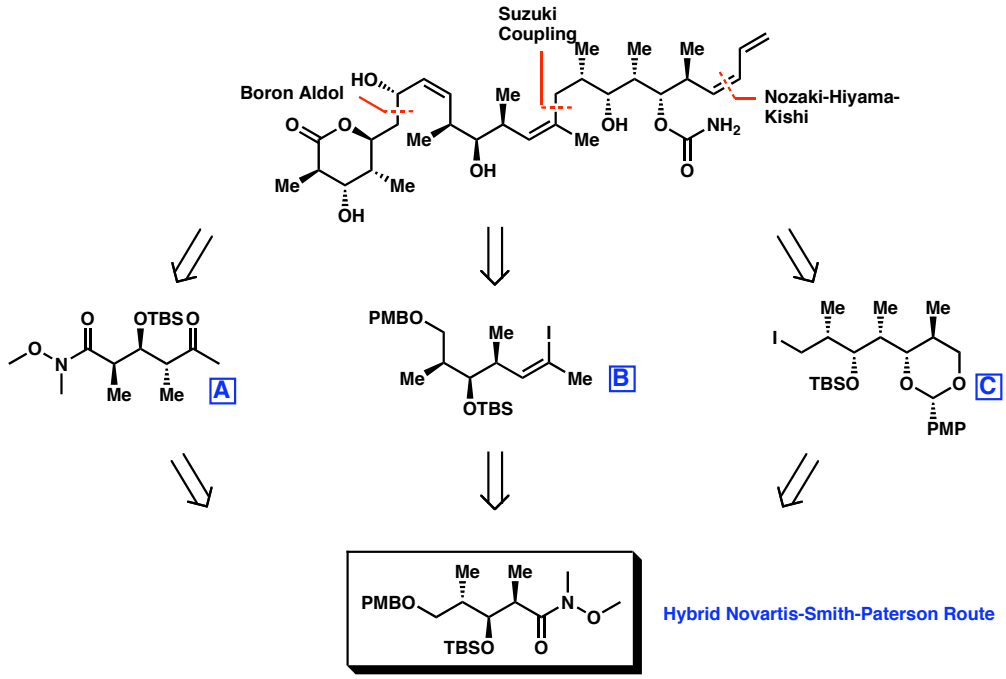


(+)-Discodermolide

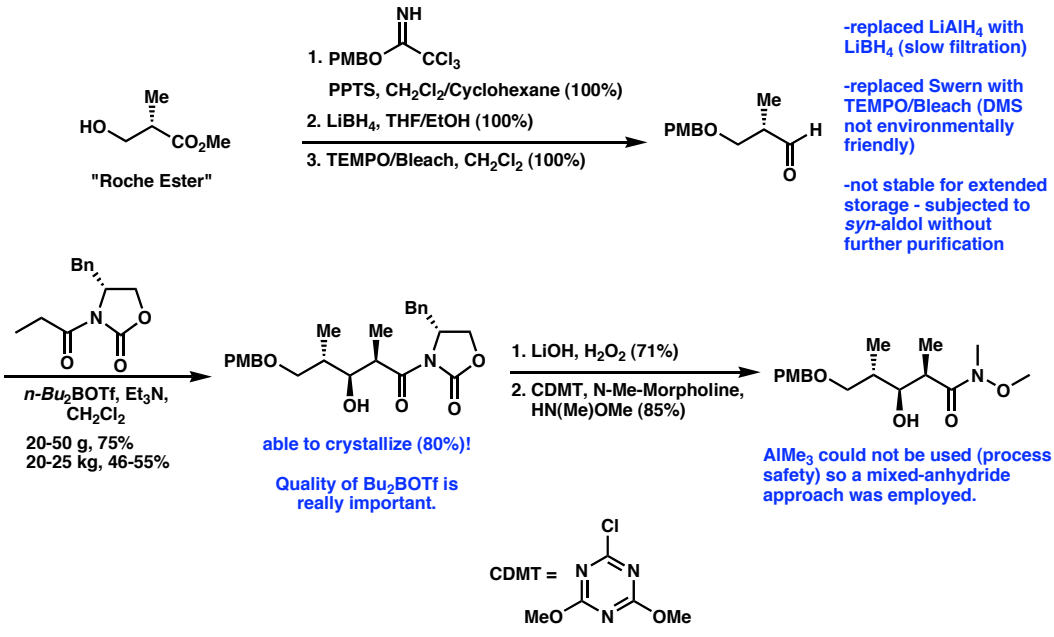
- Boron-Aldol works on gram scale
- Li-enolate produces opposite config. (Felkin-Anh induction from aldehyde)

Novartis Process Group: Scale-Up Route
(Phase I Clinical Trial Campaign)

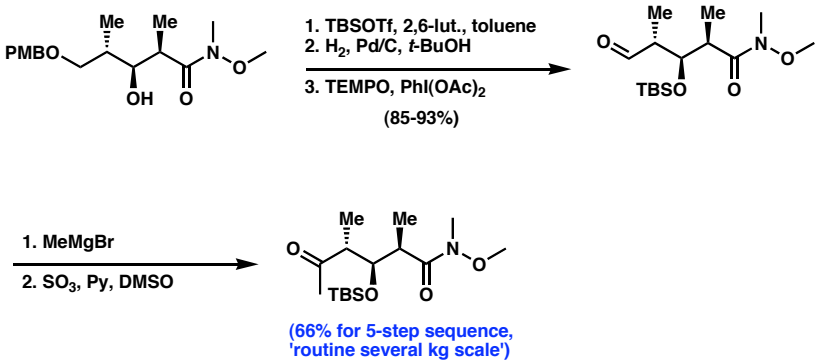
Org. Proc. Res. Dev. **2004**



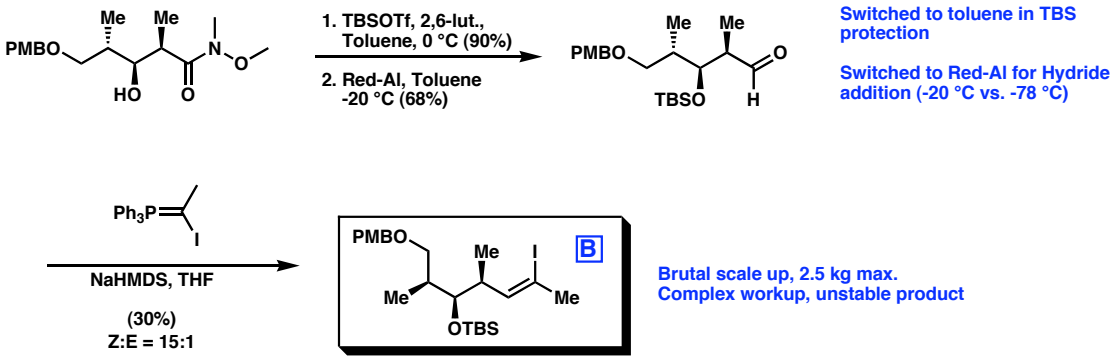
Novartis Process Group: Scale-Up Route



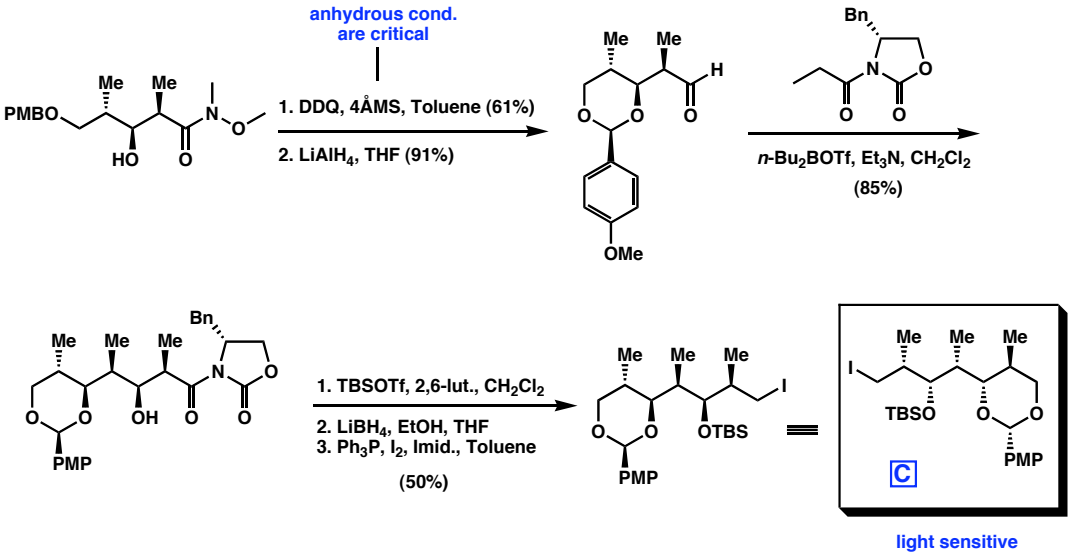
Novartis: Constructing Fragment A



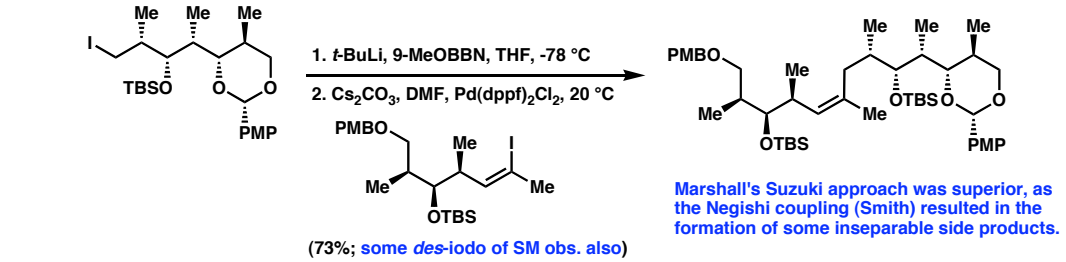
Novartis: Constructing Fragment B

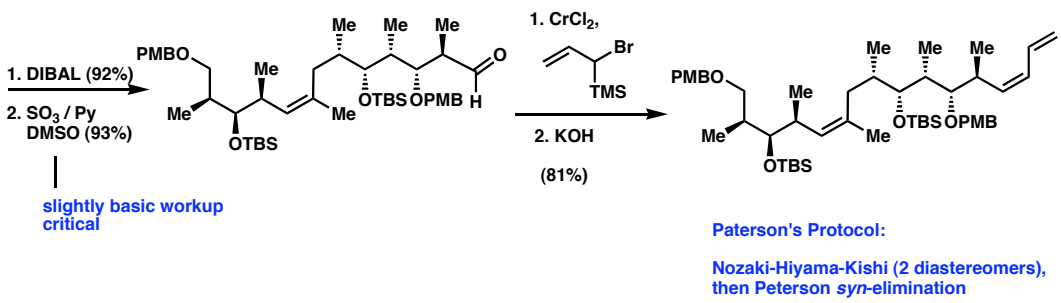


Novartis: Constructing Fragment C

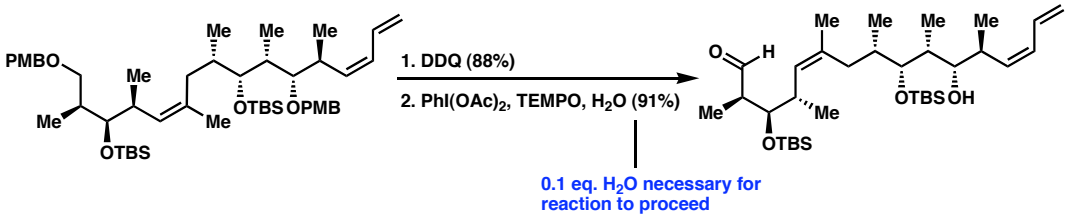


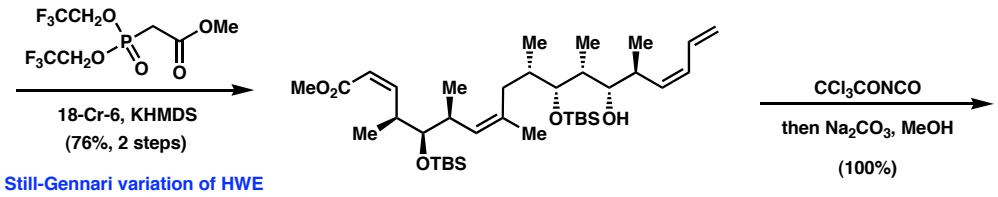
Novartis: Key Suzuki Coupling

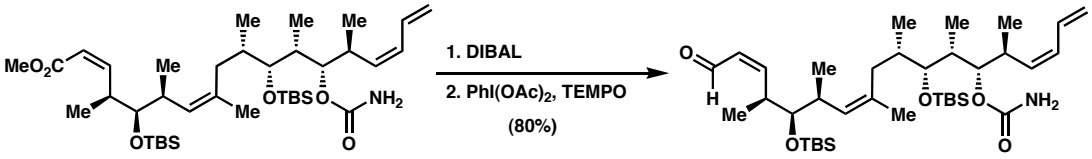




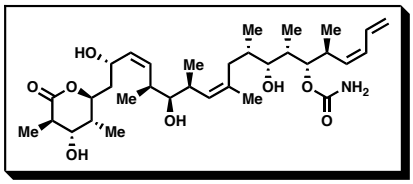
Novartis: Further Elaboration

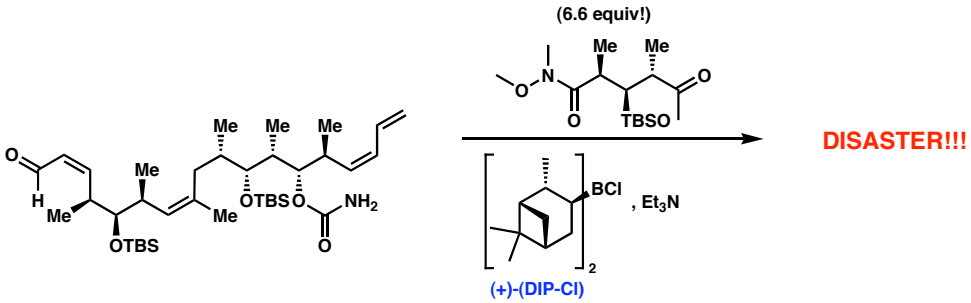






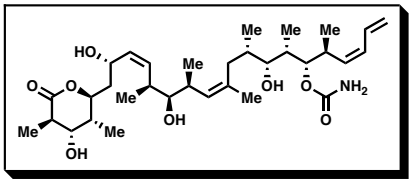
Novartis: Critical Endgame Maneuvers

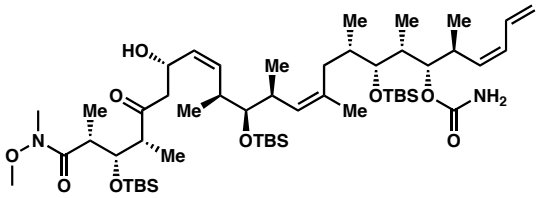




- Quality of commercial DIP-Cl was "capricious". Solved by using 70% DIP-Cl in hexane
- 4:1 epimer mixture at 250 mg scale (45%), but 23% on 50g! The problem was identified as the direct reduction of the aldehyde.
- They determined the cause of reduction was incomplete enolization. Changing to 24 hrs worked better on small scale (50% yield), but again disaster on larger scale.
- They determined that the workup (peroxide, silica gel) were lowering the yield. A quick aqueous workup was performed instead, and purification by reverse-phase silica gel led to reproducible 50-55% yields.
- Epimer can be recycled and used to make the final product.

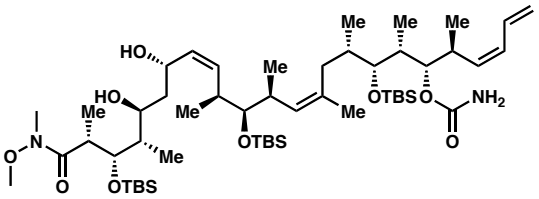
Novartis: The Grand Finale!





$Me_4N(OAc)_3BH$

(75%)



Panic broke out on the final step when they realized that the > 99% HPLC pure final product in solution registered an impurity around 8% after crystallization!

HCl / MeOH

(70%)

Discodermolide, 60 g!

Totals:

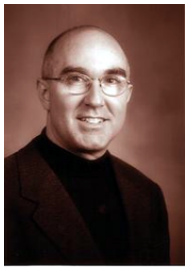
43 chemists
17 chromatographic purifications
20 months to complete
(~1 step / 2 weeks)

The Afterglow of the Novartis Synthetic Campaign

Ian Paterson

Amos Smith, III

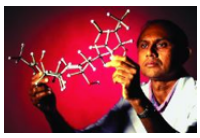
Stuart Schreiber



Stuart Mickel

NOVARTIS

Sarath Gunasekera (Isolation)



"Spectacular...It's probably the best piece of synthetic work from an industrial company"
-Steven Ley (Cambridge, UK)

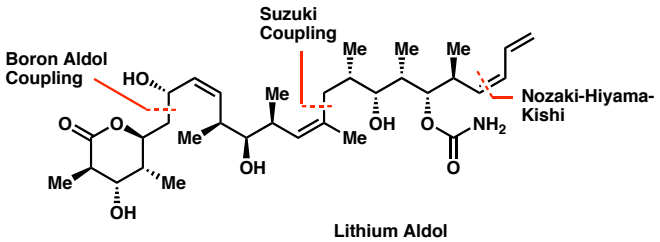
"Some 3,000 kg of the sponge, a quantity that probably does not exist, would have been needed to deliver 60 g"
-Stuart Mickel

"Clearly, the Novartis synthesis is a wonderful accomplishment, demonstrating that if a new drug candidate is sufficiently valuable, synthetic chemists will rise to the challenge of developing a viable synthetic approach no matter how complex the structure"
-Amos Smith, III

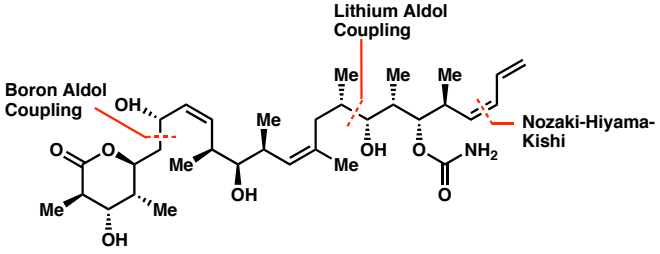
"On a positive note, this project was a first for Novartis, and its progress was avidly followed by the entire department who were all interested in the *disco*".
-Novartis

Summary of Routes Used

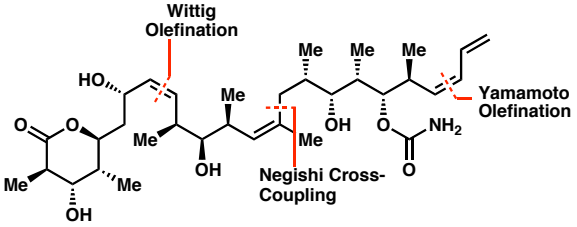
Novartis:



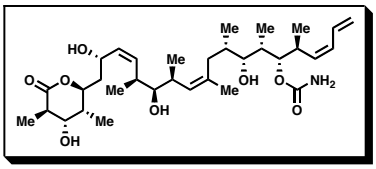
Paterson:



Smith:



What Makes A Great Total Synthesis?



Amos B. Smith, III:

-Clever Use of 'Common Precursor'
-Prepared 1 g as proof-of-concept

Smith G1:

A: 14%, 19 steps
B: 19%, 8 steps
C: 22%, 11 steps

Common Steps: 11
Total for Fragments: 27

Finish: 3%, 13 steps

Smith G2:

A: 25%, 13 steps
B: 25%, 8 steps
C: 30%, 11 steps

Common Steps: 11
Total for Fragments: 21

Finish: 20%, 13 steps

Ian Paterson:

-Common Precursor Approach (G2)
-Effective use of boron aldol reaction to assemble molecule
-Substrate-controlled creation of stereocenters (no auxilliaries)

Paterson G1:

A: 46% 10 steps
B: 43% 10 steps
C: 43% 12 steps

Common Steps: 0
Total for Fragments: 32

Finish: 21%, 13 steps

Paterson G2:

A: 40%, 11 steps
B: 24%, 11 steps
C: 28%, 13 steps

Common Steps: 11
Total for Fragments: 24

Finish: 19%, 12 steps

Novartis:

-Preparation of 60 grams!

Novartis:

A: 22%, 11 steps
B: 6%, 9 steps
C: 8%, 12 steps

Common Steps: 12
Total for Fragments: 20

Finish: 7%, 15 steps