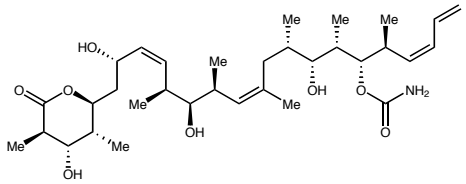
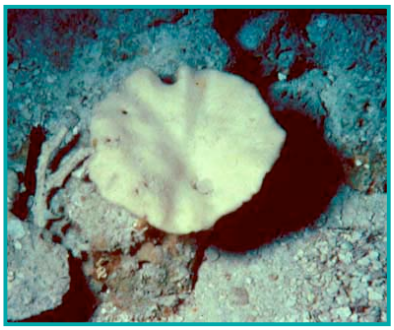
Discodermolide

A Synthetic Challenge

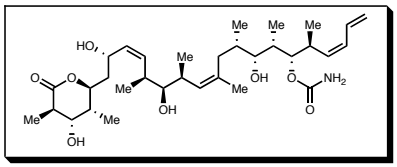




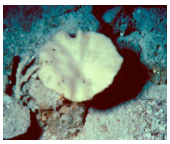
Nicole Goodwin
MacMillan Group Meeting
April 21, 2004

Discodermolide

Isolation and Biological Activity

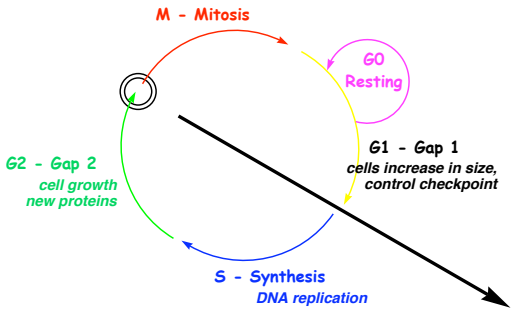


- Isolated in 1990 by the Harbor Branch Oceanographic Institution from the Caribbean deep-sea sponge *Discodermia dissoluta*

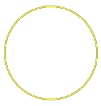


- Not practical to produce discodermolide from biological sources
  - 0.002% (by mass) isolation from frozen sponge
  - must be deep-sea harvested at a depth in excess of 33 m
- Causes cell-cycle arrest at the G_2/M phase boundary and cell death by apoptosis
- Member of an elite group of natural products that act as microtubule-stabilizing agent and mitotic spindle poisons
  - Taxol, epothilones A and B, sarcodictyin A, eleutherobin, laulimalide, FR182877, peloruside A, dictyostatin
- Effective in Taxol-resistant carcinoma cells
  - presence of a small concentration of Taxol amplified discodermolide's toxicity by 20-fold
  - potential synergies with the combination of discodermolide with Taxol and other anticancer drugs
- Licensed by Novartis from HBOI in 1998 as a new-generation anticancer drug

Cell Apoptosis

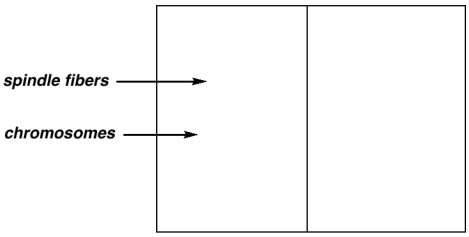


- Discodermolide disrupts the G2/M phases of the cell cycle.
- Discodermolide, like Taxol, inhibits microtubule depolymerization by binding to tubulin.
- no microtubules = no spindle fiber formation



Pacitaxol binding to tubulin dimer

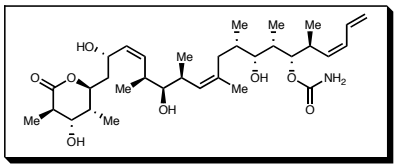
Kalesse, M. *ChemBioChem.* **2000**, *1*, 171.



Nasmyth, K.; Peters, J.-M.; Uhlmann, F. *Science.* **2000**, *288*, 1379.

Discodermolide

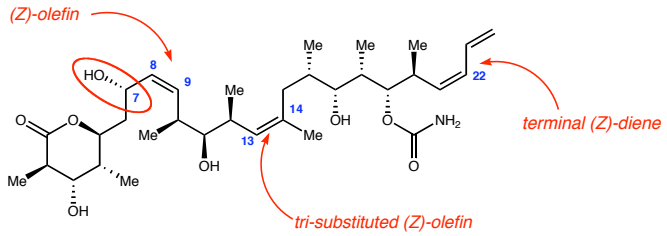
Isolation and Biological Activity



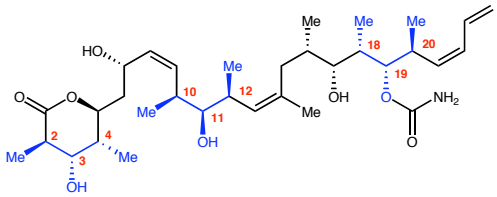
- Considerable synthetic effort to produce discodermolide because of dearth of biological supply
  - Taxol is semi-synthesized from an intermediate extracted from the European Yew tree
  - the epothilones are obtained from fermentation
- Several total syntheses and numerous fragment syntheses
  - 1993 - Schrieber
  - 1995 - Smith
    1998 - Smith, second generation
  - 1997 - Myles (UCLA)
  - 1998 - Marshall (UVa)
  - 2000 - Paterson
- Novartis synthesis is a combination these total synthesis
  - Smith - fragment syntheses from a common precursor (CP)
  - Marshall - β-alkyl Suzuki coupling of C14 to C15
  - Paterson - endgame

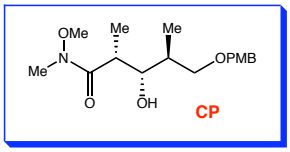
Discodermolide

A Synthetic Challenge



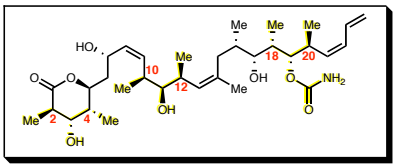
- Repeating stereotriad from common precursor (CP)





Discodermolide

Outline



- Paterson Synthesis (1998, 2001)
  - selectivity from intrinsic bias of molecule
  - boron-mediated *anti* Aldols
  - Claisen rearrangement to set C13 olefin
  - Nozaki-Hiyama/Petersen elimination - diene formation
  - selective reductions at C7 or C5

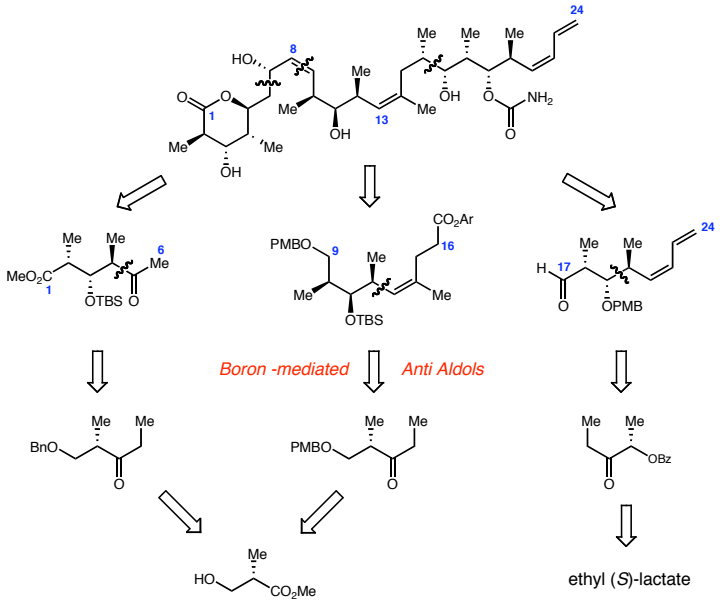
- Smith Synthesis (1995, 2003)
  - stereotriad from a common precursor (CP) - Evans aldol
  - Negishi coupling at C14
  - Yamamoto diene formation
  - Wittig olefination at C8 - first and second generation

- Marshall Synthesis (1998)
  - Allenylstannane additions to chiral aldehydes for stereotriads
  - β-alkyl Suzuki coupling with vinyl iodide

- Novartis synthesis - over 60 g produced!

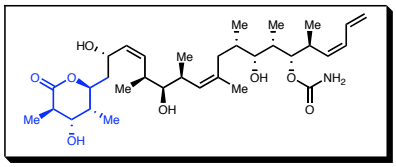
Paterson 2001

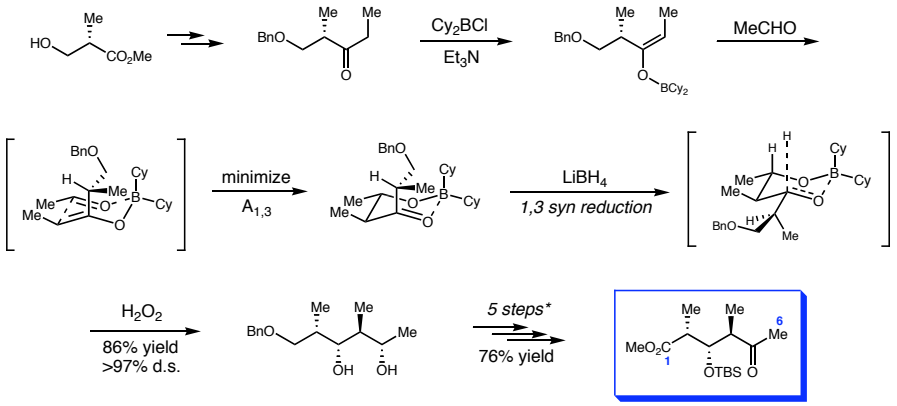
Retrosynthesis



Paterson 2001

Preparation of C_1 to C_6 Fragment

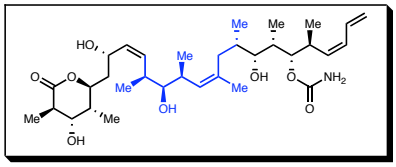


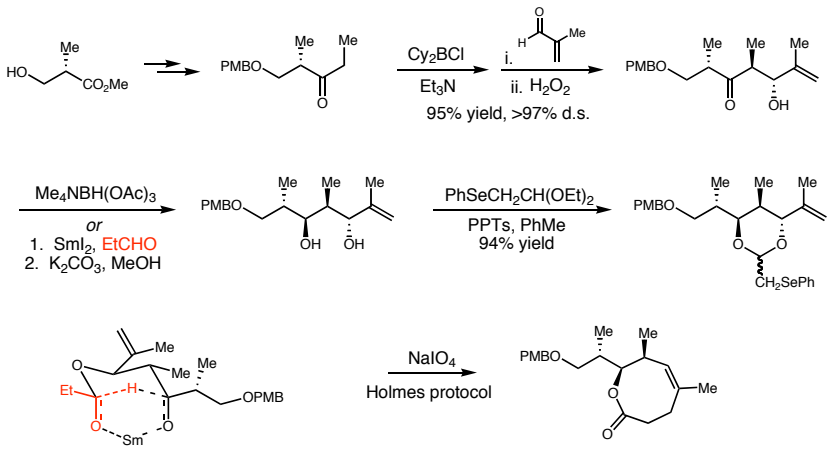


* 1. TBSOTf 2. CSA, MeOH/CH_2Cl_2. 3. $Pd(OH)_2/C$, H_2, EtOH. 4. Swern. 5. *i.* $NaClO_2$. *ii.* CH_2N_2.

Paterson 2001

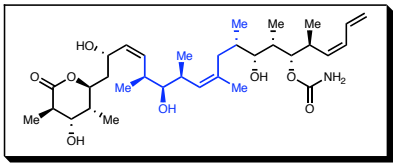
Preparation of C_9 to C_{18} Fragment

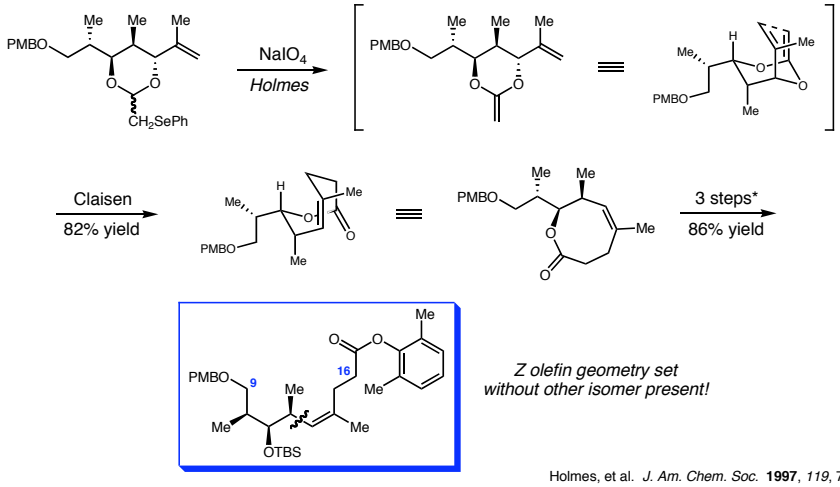




Paterson 2001

Ring Expansion Claisen Rearrangement





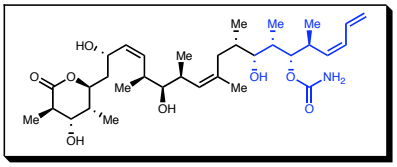
Z olefin geometry set without other isomer present!

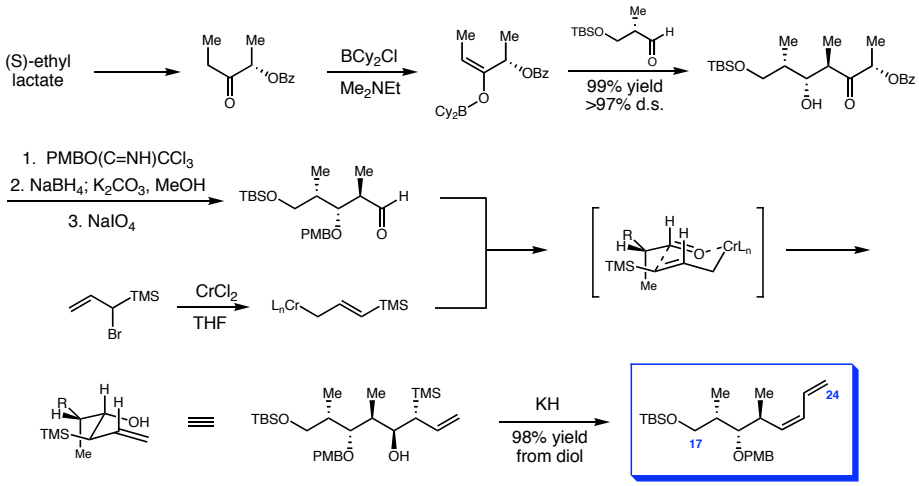
Holmes, et al. *J. Am. Chem. Soc.* **1997**, *119*, 7483

* 1. KOH, MeOH. 2. 2,6-Me_2phenol, DCC, DMAP. 3. TBSOTf

Paterson 2001

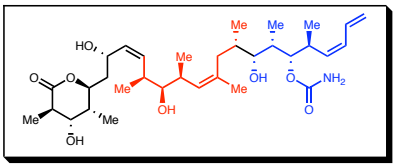
C_{17} to C_{24} Fragment

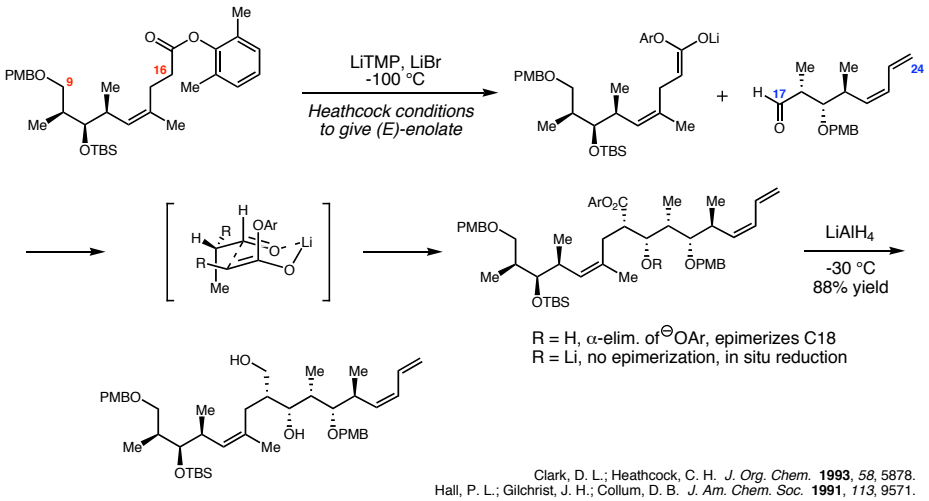




Paterson 2001

C_{17} to C_{24} and C_9 to C_{16} Fragment Union by a syn *Aldol*



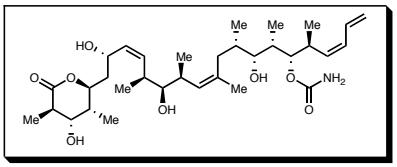


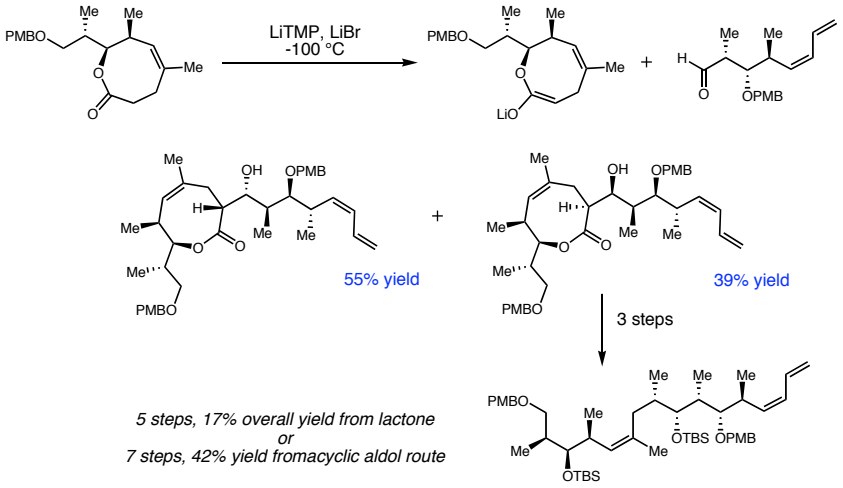
R = H, α-elim. of $^{\ominus}$OAr, epimerizes C18
R = Li, no epimerization, in situ reduction

Clark, D. L.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5878.
Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571.

Paterson 2001

Alternate Syn Aldol Approach is Unsuccessful

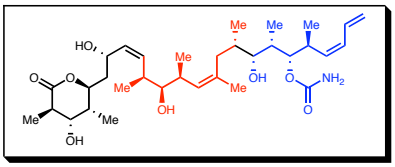


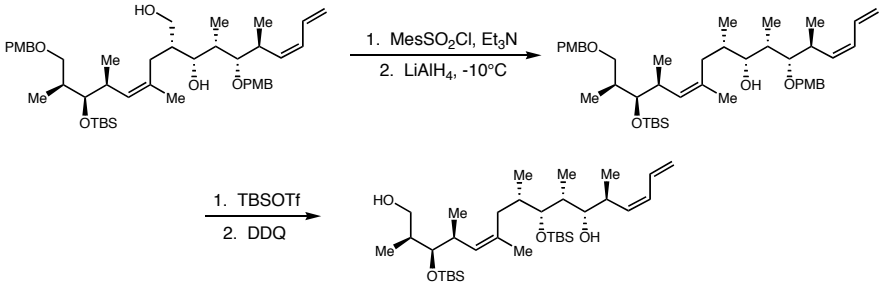


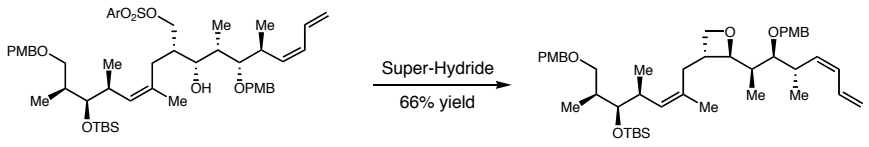
5 steps, 17% overall yield from lactone
or
7 steps, 42% yield fromacyclic aldol route

Paterson 2001

Finishing the C_9 to C_{24} Fragment

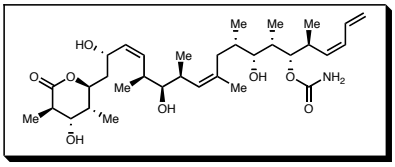


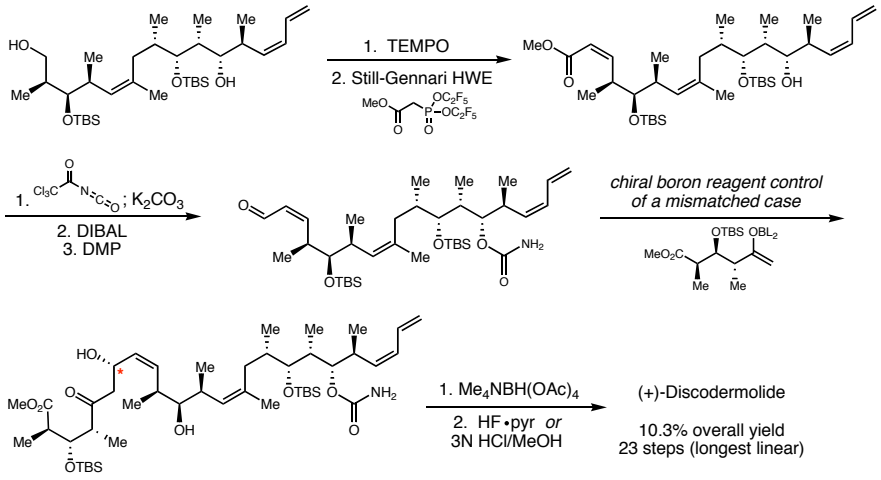




Paterson 2001

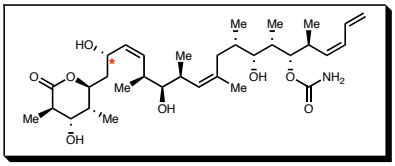
Final Coupling at C_7

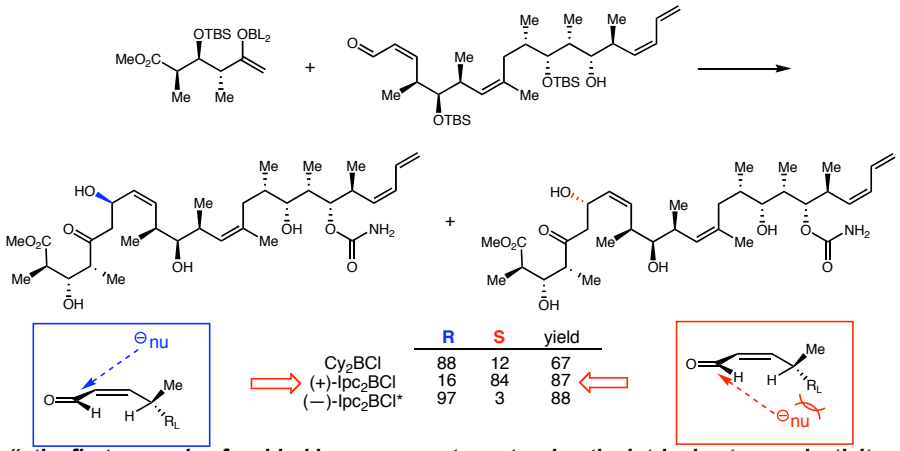




Paterson 2001

Chiral Boron Reagent Addition

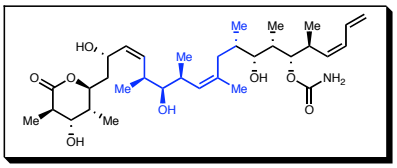


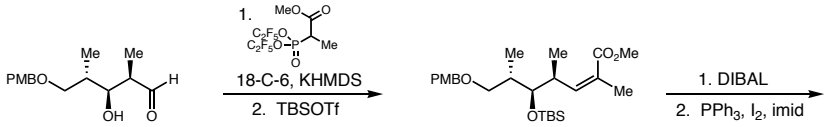


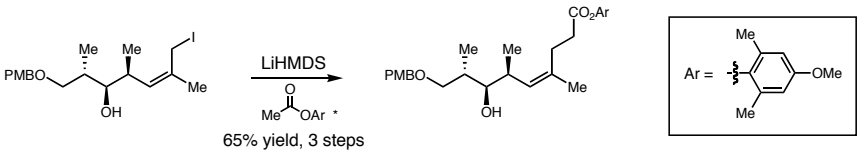
"..the first example of a chiral boron reagent overturning the intrinsic stereoselectivity of a complex aldol coupling between chiral carbonyl compounds"

Paterson 2003, Second Generation

Tri-substituted olefin



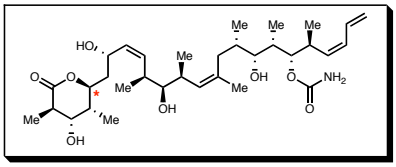




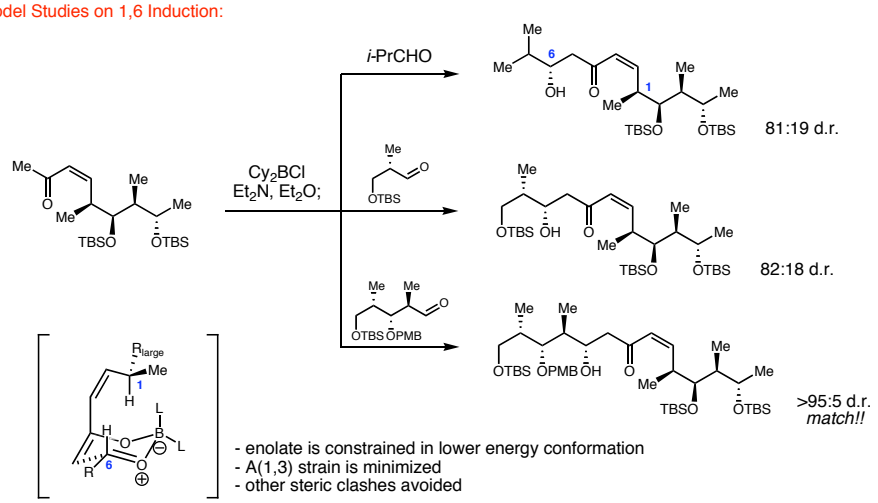
* the electron-donating 4-OMe aryl ester was needed to alkylate the iodide, no loss in yields for subsequent steps in comparison to previous route

Paterson 2003, Second Generation

Remote 1,6-Asymmetric Induction in Aldol Coupling



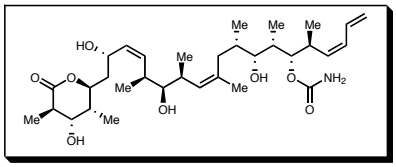
Model Studies on 1,6 Induction:

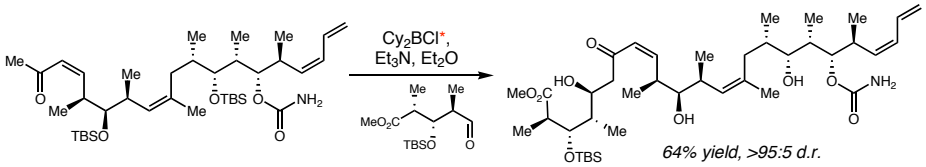


- enolate is constrained in lower energy conformation
- A(1,3) strain is minimized
- other steric clashes avoided

Paterson 2003, Second Generation

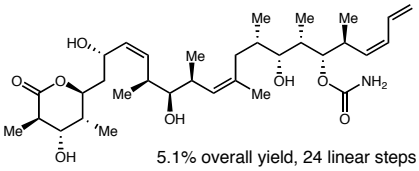
Remote 1,6-Asymmetric Induction in Aldol Coupling on Real System





1. AcOH, THF/H_2O
2. K-Selectride
3. HCl, MeOH

68% yield, 3 step
97:3 d.r. on reduction

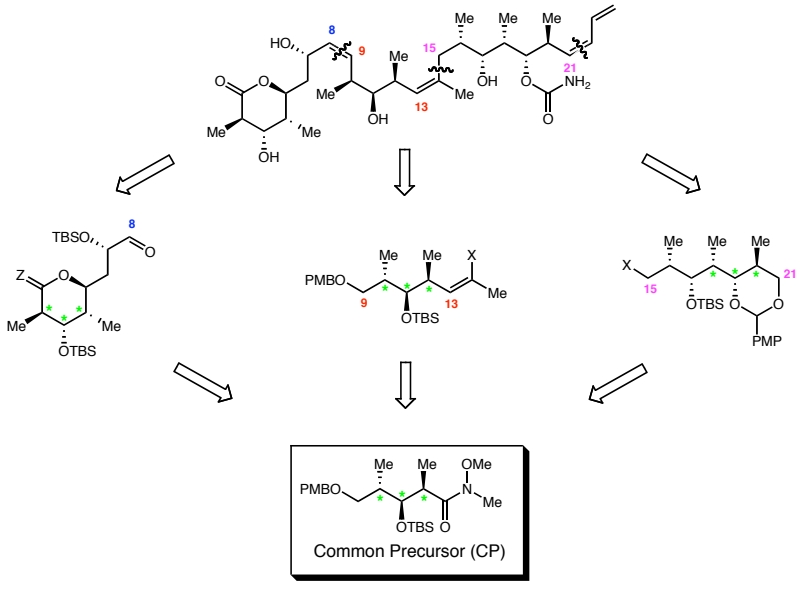


5.1% overall yield, 24 linear steps (35 total)

previous coupling: 5:1 d.r. for Aldol
present: >19:1 d.r. for Aldol

Smith 1995

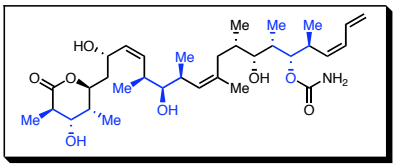
Retrosynthesis



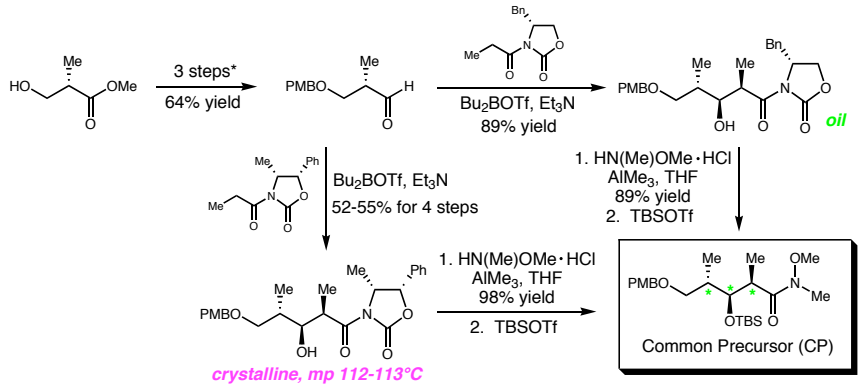
Smith, A. B. III.,et al. *J. Am. Chem. Soc.* **1995**, *117*, 12011.
Smith, A. B. III.,et al. *J. Am. Chem. Soc.* **2000**, *122*, 8654.

Smith 1995

Synthesis of Common Precursor



- Smith's approach to proceed from a common precursor was adopted by Novartis
- Utilizes Evans oxazolidinone Aldol chemistry to set the stereotriad

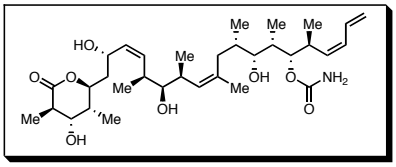


- Yield of norephedrine-based Aldol was 64-70% on 60-70 g scales, 55% for all 4 steps with recrystallization, auxiliary recovery was 80-90%

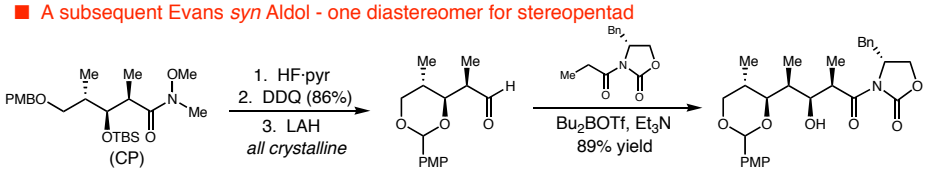
* 1. $PMBO(C{=}NH)CCl_3$, PPTs. 2. LAH. 3. Swern.

Smith 1995

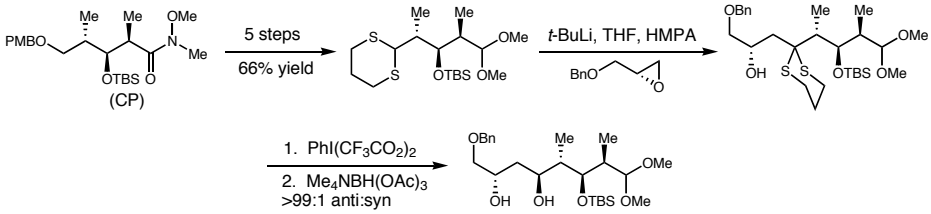
Elaboration of Common Precursor



- Polypropionate elaboration for C_{15}-C_{21}
- A subsequent Evans *syn* Aldol - one diastereomer for stereopentad

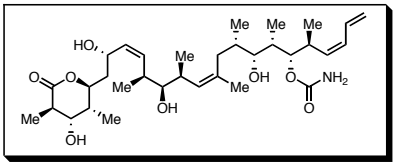


- A diastereoselective diathiane addition for C_1-C_8

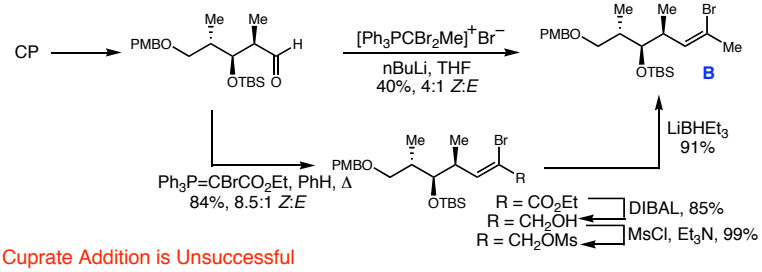


Smith 1995

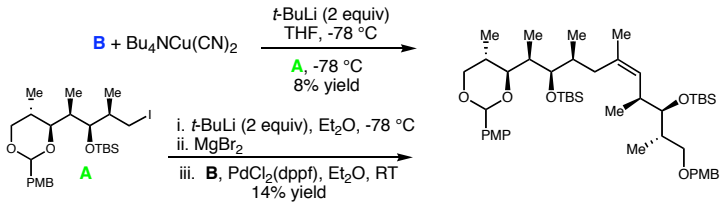
Elaboration of Common Precursor for Trisubstituted Olefin



■ Vinyl Bromide for Cuprate Addition to alkyl iodide

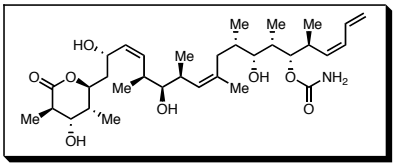


■ Cuprate Addition is Unsuccessful

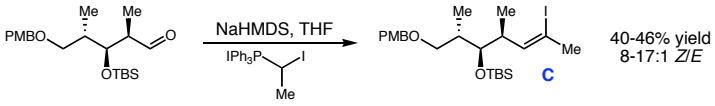


Smith 1995

Elaboration of Common Precursor for Trisubstituted Olefin



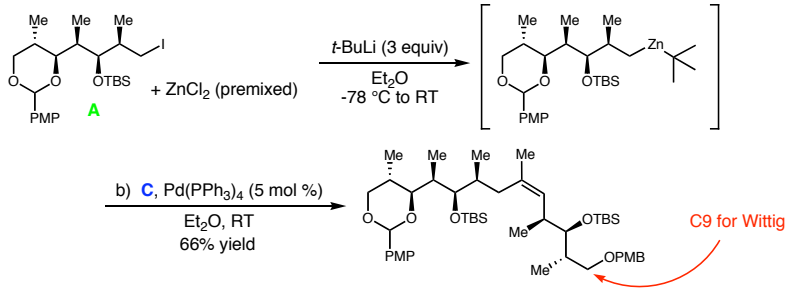
■ Vinyl Iodide for Negishi coupling to alkyl iodide



Zhao-Wittig: Chen, J.; Wang, T.; Zhao, K. *Tet. Lett.* **1994**, *35*, 2827.

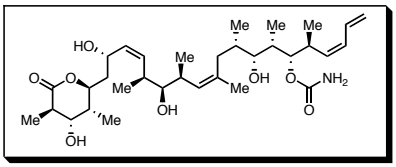
- loss of I in **C** is major byproduct due to poor solubility of iodine in THF, addition of 0.1M I_2 in THF circumvents this

■ Negishi coupling is efficient

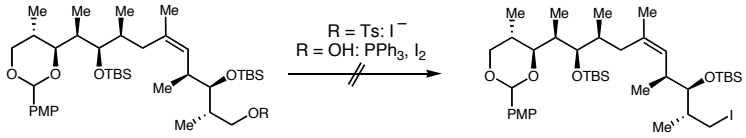


Smith 1995

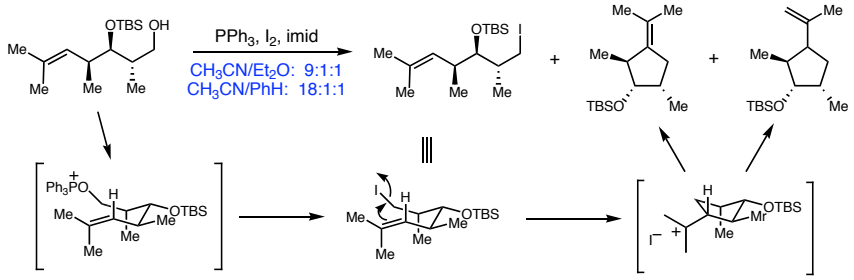
Wittig Olefination for Cis C_8-C_9 *Olefin*



- Problems in making alkyl iodide



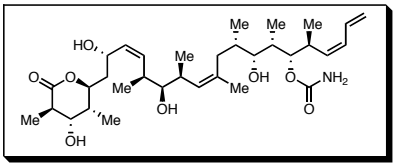
- Turn to model systems and solvent effects



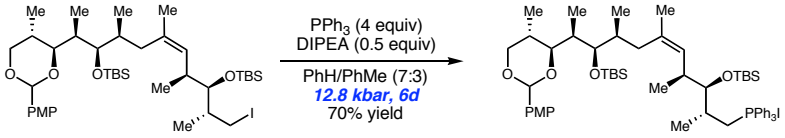
- More polar solvents promote cyclization (MeCN or MeCN/Et_2O), less polar solvents favor iodide

Smith 1995

Wittig Olefination for Cis C_8-C_9 *Olefin*

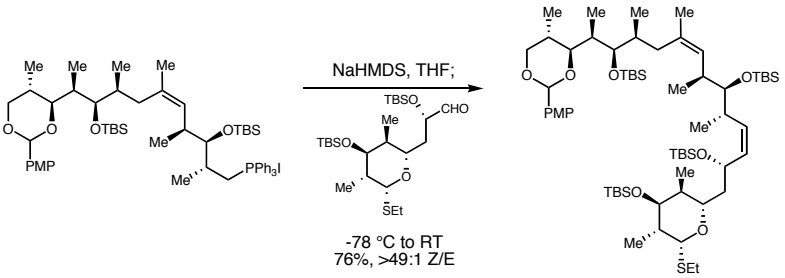


- High pressure necessary to form Wittig



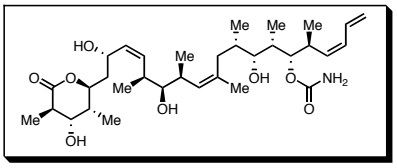
- addition of base necessary to absorb HI that forms and causes decomposition of starting iodide

- Wittig reaction proceeds smoothly

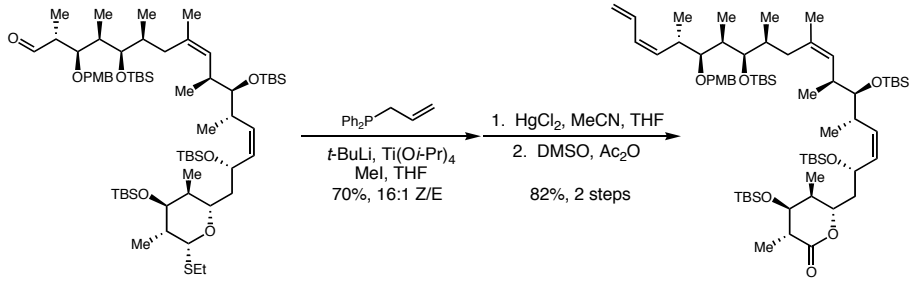


Smith 1995

First Generation Endgame



■ Installation of (Z)-diene by Yamamoto protocol followed by thiol oxidation and deprotection



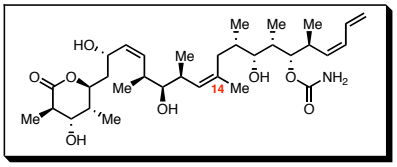
(—)-Discodermolide

1.043 g after reacrystallization
24 steps, longest linear
6% overall yield

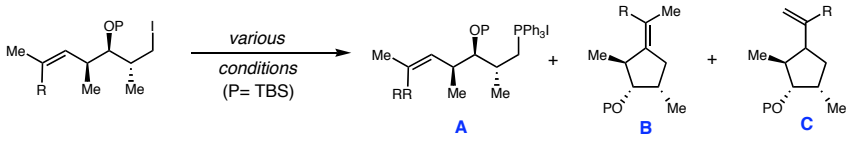
■ Second generation synthesis changes the order of steps and eliminates dithane approach to lactone in favor of an allylsilane Ti-mediated addition to the CP

Smith 2003

Third Generation Synthesis Approaches High Pressure Wittig



■ Without high pressure, the same byproducts emerge as with the original iodination

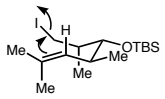


■ Absense of methyl at C_{14} leads to highly efficiently olefination (99% yield)

■ Choice of protecting group at C_{11} is crucial (model studies done with R = Me at 100 °C)

P	**A** (%)	**B/C** (%)
Ac	59	41
SEM	63	34
BOM	69	30
MOM	69	24
H	62	38
TBS	35	63

■ Explained by cyclization transition state

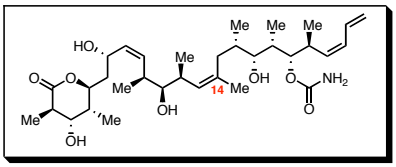


- larger OP might promote a puckering of the TS chair, giving a predisposition to cyclization, a "reactive rotamer effect"
- smaller OP increase the rate of SN_2 displacement by PPh_3

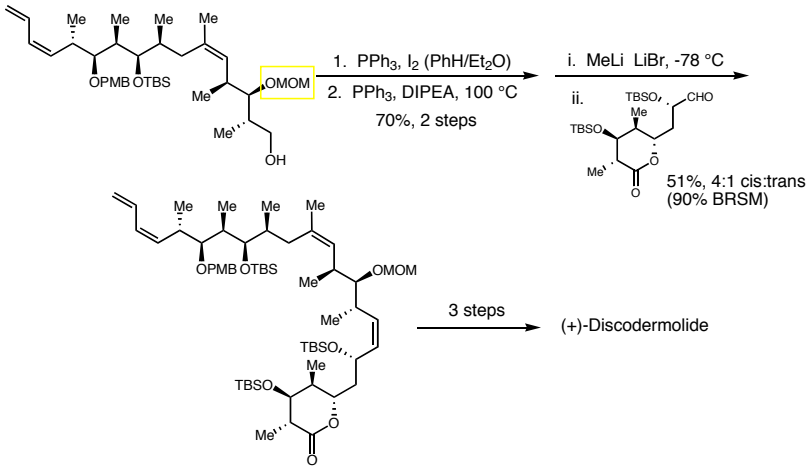
Smith, A. B. III.; Freeze, B. S.; Brouard, I.; Hirose, T. *Org. Lett.* **2003**, *5*, 4405.

Smith 2003

Third Generation Synthesis Approaches High Pressure Wittig



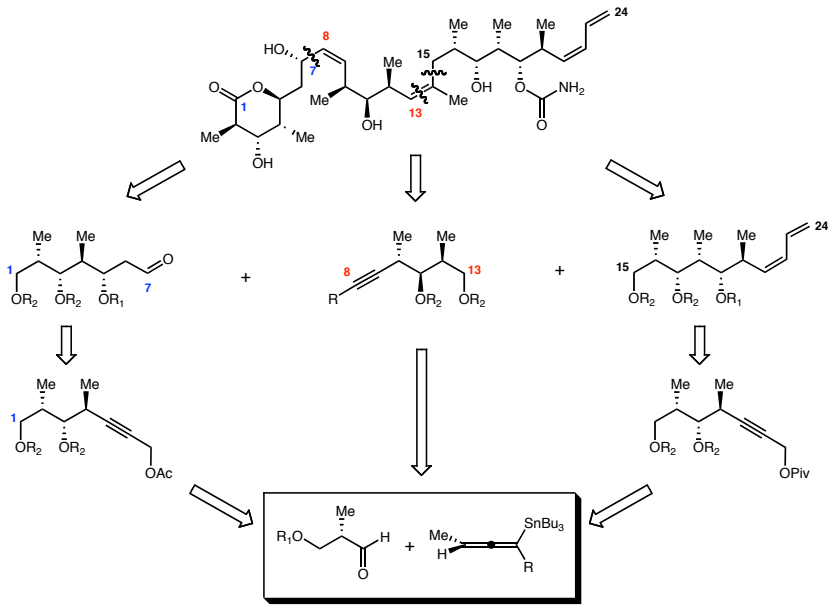
- Newer synthesis amenable to larger scale without high pressure



Smith, A. B. III.; Freeze, B. S.; Brouard, I.; Hirose, T. *Org. Lett.* **2003**, *5*, 4405.

Marshall 1998

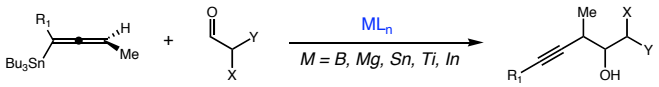
Retrosynthesis



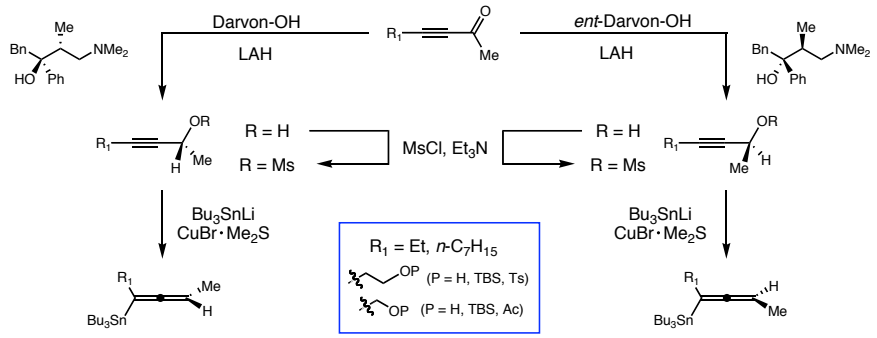
Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.

Diastereoselective Additions of Chiral Allenyl Stannanes

Marshall reports diastereoselective additions of allenyl stannanes to aldehydes by S_E' addition



- Preparation of Chiral Allenyl Stannanes in about 90% e.e.

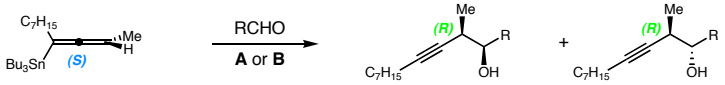


- Allenyl stannanes are stable to storage, silica, and excess cuprate without racemization or isomerization
- Cuprate addition is highly ANTI selective to give one allene isomer

Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1992**, *57*, 1242.
Ruitenberg, K. et al. *J. Organomet. Chem.* **1983**, *241*, 417.

Diastereoselective Additions of Chiral Allenyl Stannanes

- Achiral aldehyde additions - not so useful



A: BF_3 OEt_2, CH_2Cl_2, -78 °C. **B**: $MgBr_2$ OEt_2, CH_2Cl_2, -23 to 0 °C

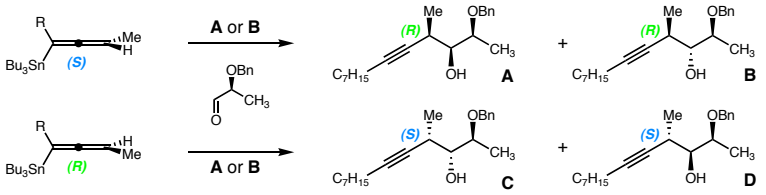
R	conditions	yield %	syn:anti
C_6H_{13}	A	83	39:61
	B	56	66:34
i-Pr	A	80	99:1
	B	68	88:12
t-Bu	A	92	99:1

- Unbranched alkyl aldehydes are not selective
- Achiral aldehydes not useful for anti additions
- Move to α-substituted chiral aldehydes - more rigidity to transition state

Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1992**, *57*, 1242.
Ruitenberg, K. et al. *J. Organomet. Chem.* **1983**, *241*, 417.

Diastereoselective Additions of Chiral Allenyl Stannanes

- Chiral aldehyde additions



(R/S) - R	conditions	yield %	A:B	C:D
(*S*) - CH_2OAc	A	95	68:32	
	B	97	>99:1	
(*R*) - CH_2OAc	A	97		97:3
	B	97		1:99
(*S*) - Et	A	92	87:13	
	B	98	>99:1	
(*R*) - Et	A	89		>99:1
	B	95		1:99

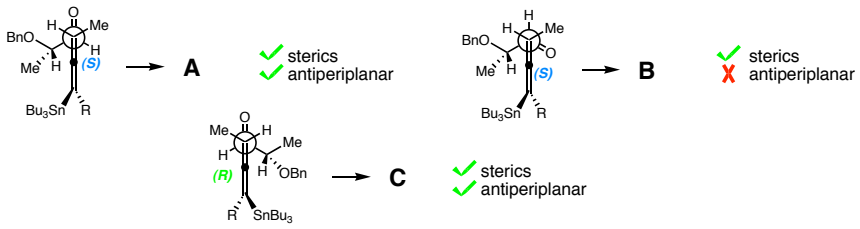
A: $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C.
B: $MgBr_2 \cdot OEt_2$, CH_2Cl_2, -23 to 0 °C

- No efficient ways to produce *anti,anti* **B**
- Selectivity governed by Felkin-Ahn (for B) or Cram-chelation (for Mg) transition states
- Anti products are rarely observed with crotylstannanes

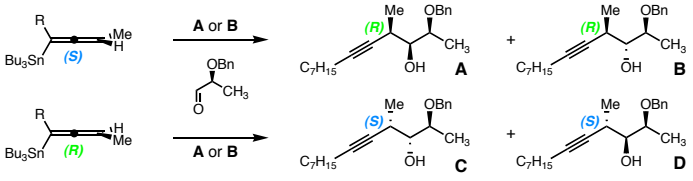
Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1992**, *57*, 1242.

Diastereoselective Additions of Chiral Allenyl Stannanes

Transition State Analysis for Non-Chelating Case with BF_3OEt_2



- Felkin-Ahn TS for *(S)*-allene is complicated by conformation mobility of the aldehyde - selectivity degradation

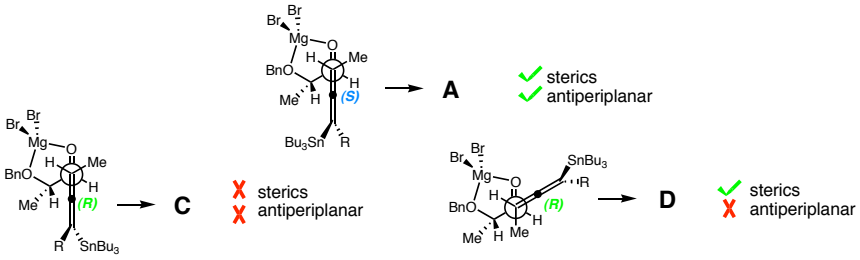


(R/S) - R	conditions	yield %	A:B	C:D
(*S*) - CH_2OAc	**A**	**95**	**68:32**	
	B	97	>99:1	
(*R*) - CH_2OAc	**A**	**97**		**97:3**
	B	97		1:99

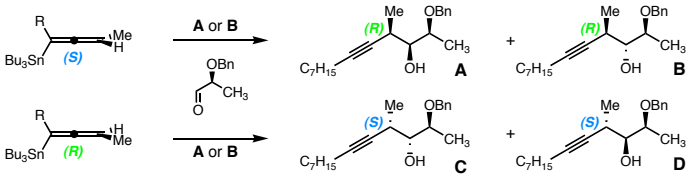
A: $BF_3 \cdot OEt_2$
B: $MgBr_2 \cdot OEt_2$

Diastereoselective Additions of Chiral Allenyl Stannanes

Transition State Analysis for Chelating Case with $MgBr_2OEt_2$



- Unfavorable steric interactions are insufficient to overcome antiperiplanar preference

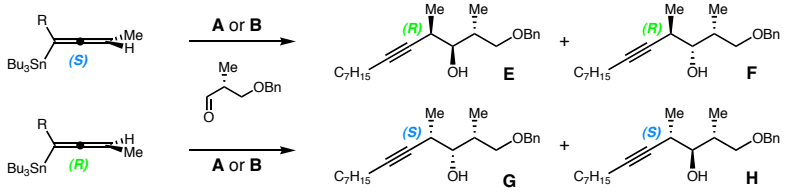


(*R*/*S*) - R	conditions	yield %	A:B	C:D
(*S*) - CH_2OAc	A	95	68:32	
	B	**97**	**>99:1**	
(*R*) - CH_2OAc	A	97		97:3
	B	**97**		**1:99**

A: $BF_3 \cdot OEt_2$
B: $MgBr_2 \cdot OEt_2$

Diastereoselective Additions of Chiral Allenyl Stannanes

- Chiral aldehyde additions



(*R*/*S*) - R	conditions	yield %	E:F	G:H
(*S*) - CH_2OAc	A	98	83:17	
	B	95	>99:1	
(*R*) - CH_2OAc	A	96		>99:1
	B	96		>99:1
(*S*) - Et	A	88	84:16	
	B	93	>99:1	
(*R*) - Et	A	92		>99:1
	B	94		50:50

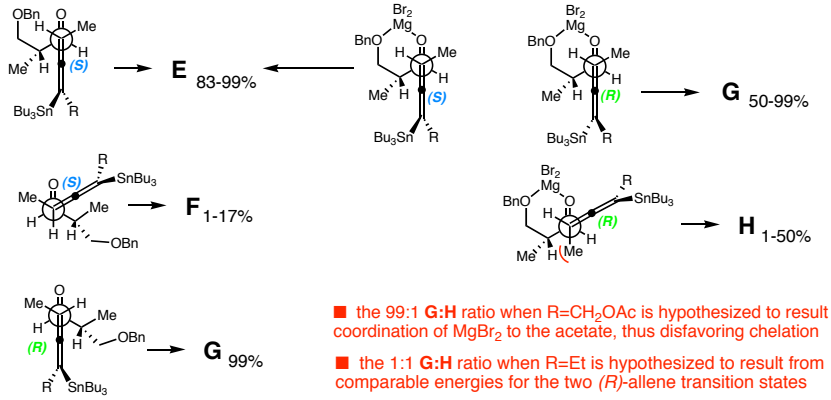
A: $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C.
B: $MgBr_2 \cdot OEt_2$, CH_2Cl_2, -23 to 0 °C

- No efficient ways to produce *anti,anti* **H** or *anti,syn* **F**
- Transition state analysis is similar to previous cases

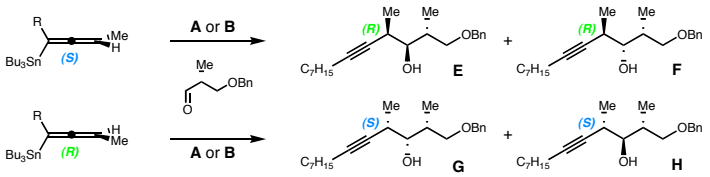
Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1992**, *57*, 1242.

*Transition States for Products **E** to **H***

(R)-*allene leads to interesting observations*



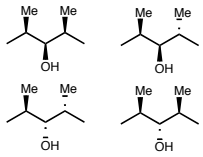
- the 99:1 **G:H** ratio when R=CH_2OAc is hypothesized to result from coordination of $MgBr_2$ to the acetate, thus disfavoring chelation
- the 1:1 **G:H** ratio when R=Et is hypothesized to result from comparable energies for the two *(R)*-allene transition states



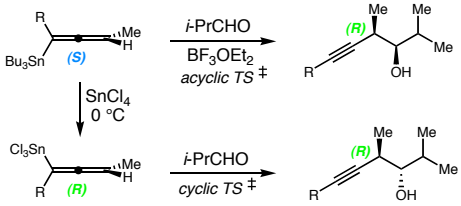
Diastereoselective Additions of Chiral Allenyl Stannanes

Inversion of Allene Stereochemistry with $SnCl_4$

- Looking for a single strategy to give all 4 stereotriads
- Previous work gives efficient syntheses of *syn,syn* and *syn,anti*
- Now define conditions for *anti,anti* and *anti,syn*



- Addition of $SnCl_4$ inverts stereochemistry of allene. Use with chiral aldehydes again for better selectivities and access to stereotriads.

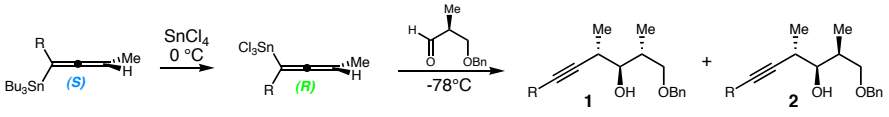


Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1992**, *57*, 1242.

Diastereoselective Additions of Chiral Allenyl Stannanes

Inversion of Allene Stereochemistry with $SnCl_4$

■ Solvent has a pronounced effect

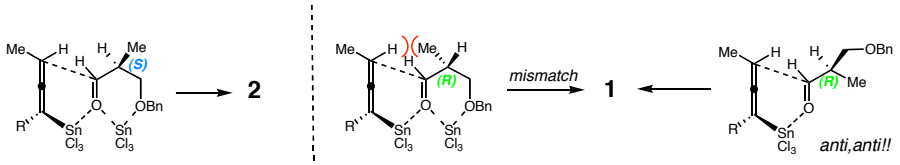


R	solvent	yield %	1 : 2
CH_2OAc	CH_2Cl_2	90	67 : 33
CH_2OAc	hexanes	91	7 : 93
C_7H_{15}	hexanes	81	1 : 99

⟸ *epimeric at aldehyde α-carbon!?!?*

$SnCl_4$ in CH_2Cl_2 leads to trace amounts of HCl

■ Cyclic transition states are very selective, and **1** is from aldehyde epimerization

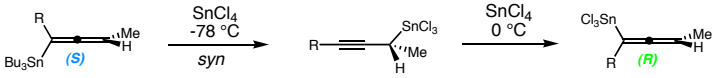


Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556.

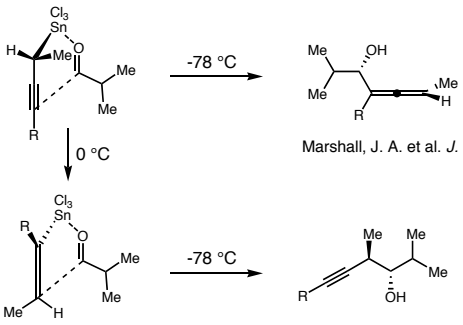
Diastereoselective Additions of Chiral Allenyl Stannanes

Inversion of Allene Stereochemistry with $SnCl_4$

■ Mechanism of allene rearrangement



■ Propargyl stannane intermediate observed experimentally



Marshall, J. A. et al. *J. Org. Chem.* **1995**, *60*, 5550

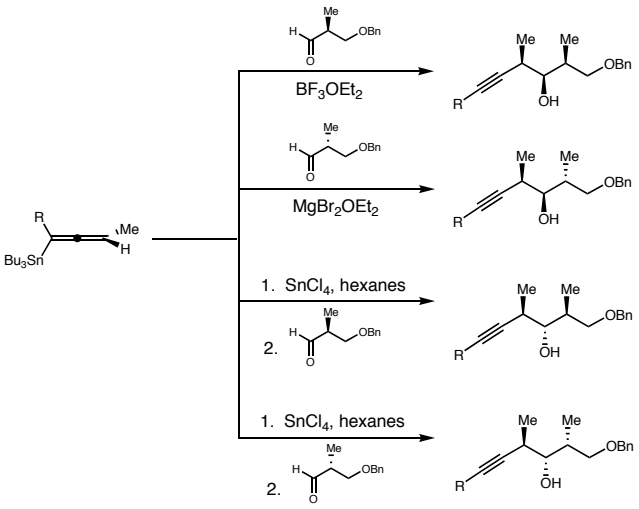
■ Reproducibility can be problematic with $SnCl_4$ - InI_3 or $SnBuCl_3$ also do allene inversion but have decreased selectivity (Marhsall, J. A.; Palovich, M. R. *J. Org. Chem.* **1997**, *62*, 2001.)

■ Allenylsilanes can also be used with $TiCl_4$ - all 4 stereotriads can be access by choice of chelating or non-chelating group on aldehyde (Marhsall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 603.)

Diastereoselective Additions of Chiral Allenyl Stannanes

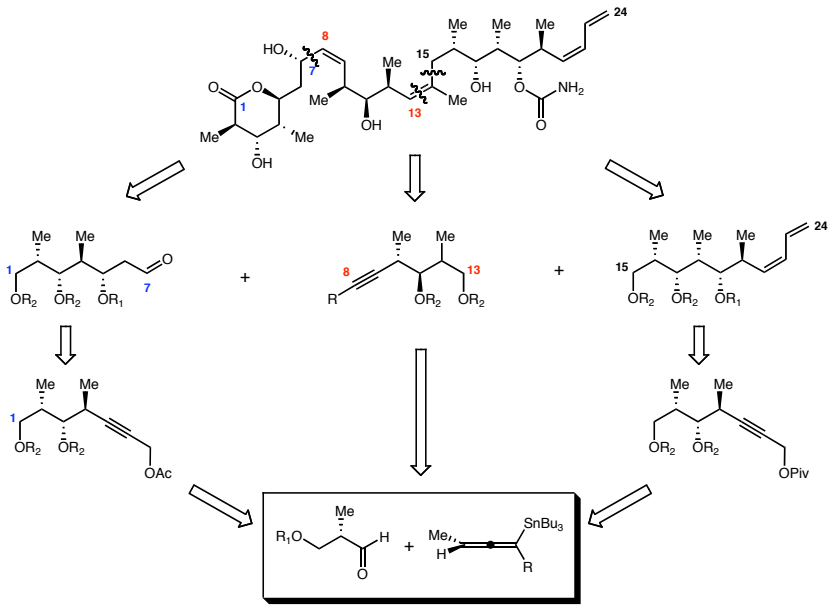
Summary

- Access to all 4 stereotriads from one allenyl stannane using reagent control



Marshall 1998

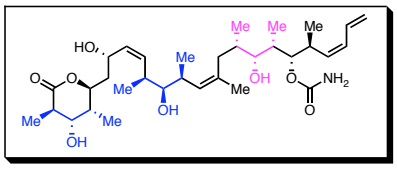
Retrosynthesis



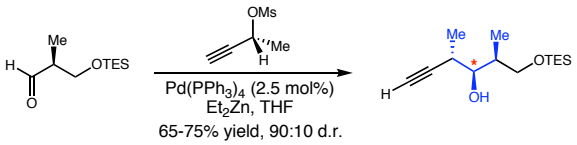
Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.

Marshall 1998

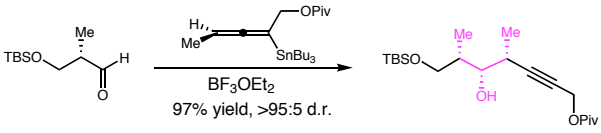
Stereotriad Syntheses



- C_2-C_4 and C_{10}-C_{12} stereotriad from new allenylzinc addition (Marshall *J. Org. Chem.* **1998**, *63*, 3812)
  - $SnCl_4$ methodology proved to be problematic in reproducibility, $BuSnCl_3$ gave 48% yield
  - did not desire to use InI_3 or $InBr_3$ in large scale syntheses



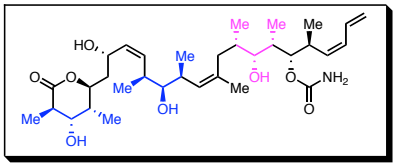
- C_{16}-C_{18} stereotriad from allenylstannane addition with BF_3OEt_2



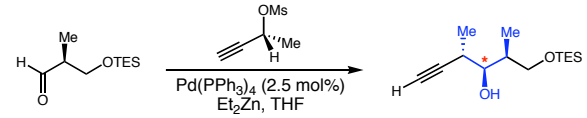
Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.

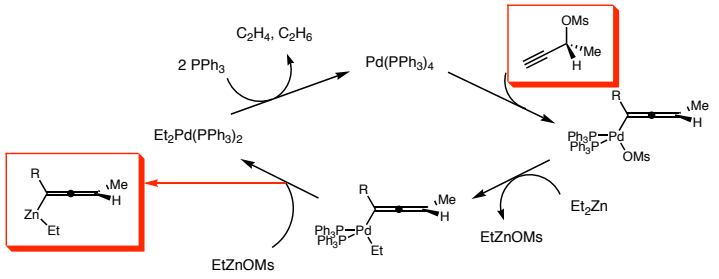
Marshall 1998

Stereotriad Syntheses



- C_2-C_4 and C_{10}-C_{12} stereotriad from new allenylzinc addition (Marshall *J. Org. Chem.* **1998**, *63*, 3812)
  - $SnCl_4$ methodology proved to be problematic in reproducibility, $BuSnCl_3$ gave 48% yield
  - did not desire to use InI_3 or $InBr_3$ in large scale syntheses

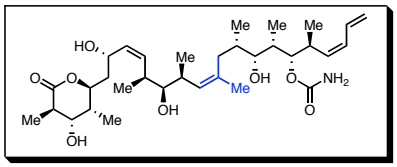




Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.

Marshall 1998

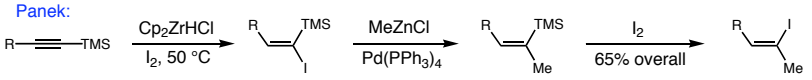
Approach to Tri-substituted olefin



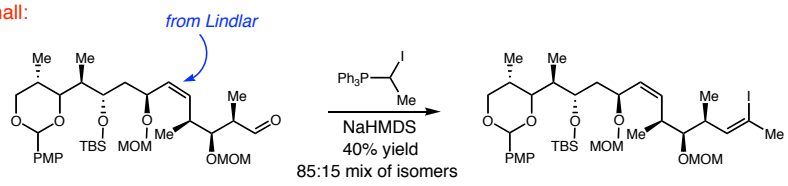
- A new approach to olefin formation - β-alkyl Suzuki coupling
- First must selectively form *(Z)*-vinyl iodide - Wittig reagent
  - Wittig reagent is low yielding and not as selective as other methods but amenable for large scale synthesis
  - Paterson's selenium reagent is toxic
  - Panek uses a large excess of Schwartz's reagent

Paterson:

Panek:



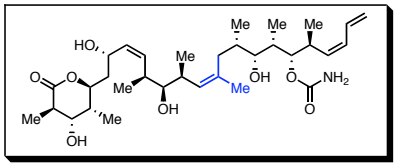
- Marshall:



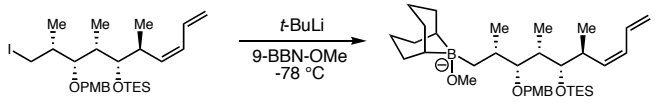
Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.

Marshall 1998

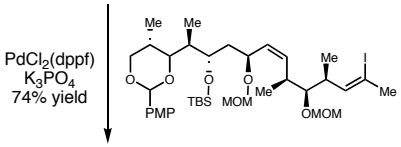
Approach to Tri-substituted olefin

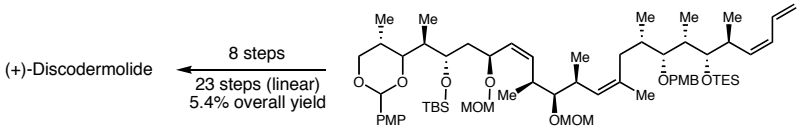


- A new approach to olefin formation - β-alkyl Suzuki coupling



- used by Novartis on a 2.5 kg scale
- Smith's Negishi coupling gave several inseparable by-products on large scale

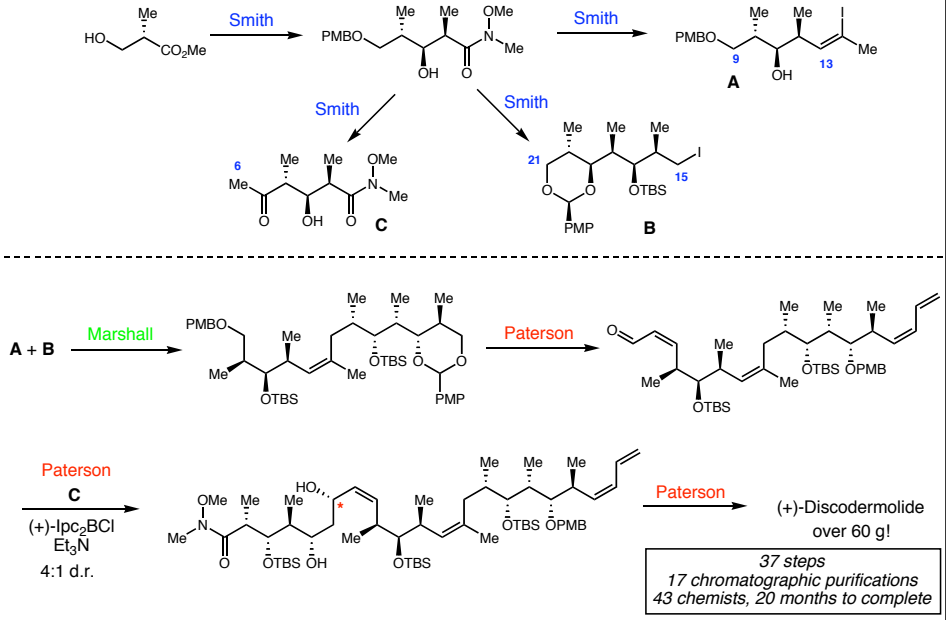




Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.

Novartis Commercial Synthesis

A mixture of Smith/Paterson/Marshall Syntheses



Summary

Discodermolide

- Several total syntheses and numerous formal syntheses
- Smith and Paterson and Marshall approaches were combined for the commercial synthesis by Novartis
- Other approaches detail novel ways to access stereotriads or stereopentad.
  - none are as efficient as the approaches described here
  - Schrieber, Myles, and Smith (2nd generation) utilizes lewis acid-mediated crotylations with allylsilanes or allyl stannanes - not useful for larger scale
- There is no practical, original way to set polypropionates for discodermolide
- Large scale preparation of discodermolide will allow for significant testing for anti-cancer activity and other health issues

Useful References

Discodermolide

- Novartis synthesis

Mickel, S. J. et al. *Organic Process Research & Development.* **2004**, *8*, 92-100.
Mickel, S. J. et al. *Organic Process Research & Development.* **2004**, *8*, 101-106.
Mickel, S. J. et al. *Organic Process Research & Development.* **2004**, *8*, 107-112.
Mickel, S. J. et al. *Organic Process Research & Development.* **2004**, *8*, 113-121.
Mickel, S. J. et al. *Organic Process Research & Development.* **2004**, *8*, 122-130.

- Paterson synthesis

Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535-9544.
Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereining, N. *Org. Lett.* **2003**,*5*, 35-38.

- Smith synthesis

Smith, A. B.; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011-12012.
Smith, A. B. III; et al. *J. Am. Chem. Soc.* **2000**, *122*, 8654-8664.
Smith, A. B. III; Freeze, B. S.; Brouard, I.; Hirose, T. *Org. Lett.* **2003**, *5*, 4405

- Marshall synthesis

Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885-5892.
Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817-823.

- Myles synthesis

Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6098-6099.
Harried, S. S.; Lee, C. P.; Yang, G.; Lee, T. I. H. *J. Org. Chem.* **2003**, *68*, 6646-6660.

- Scrieber synthesis

Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621-12622.
Hung. D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054-11080.