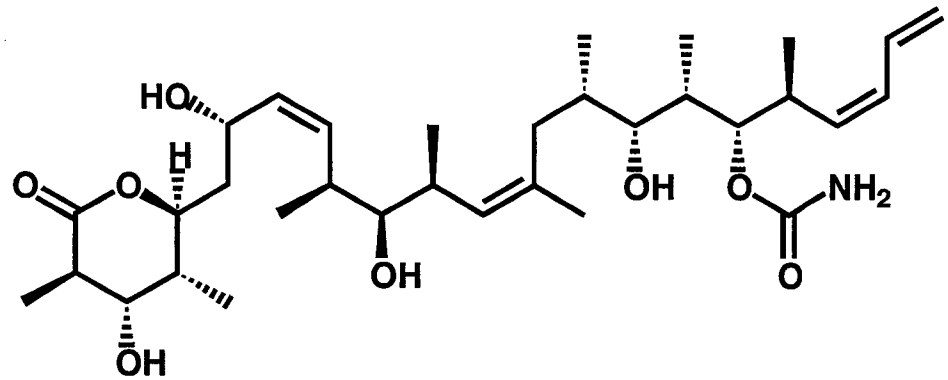
Development of an Industrial Synthesis of Discodermolide

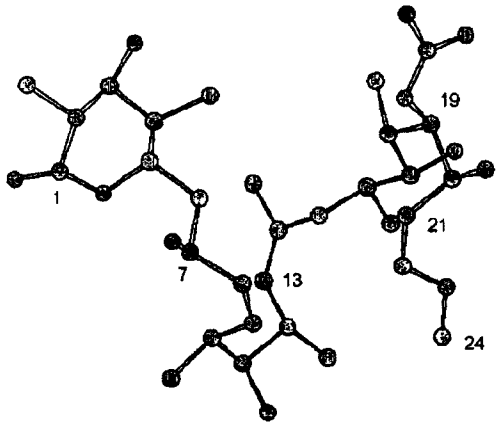


(+)-Discodermolide

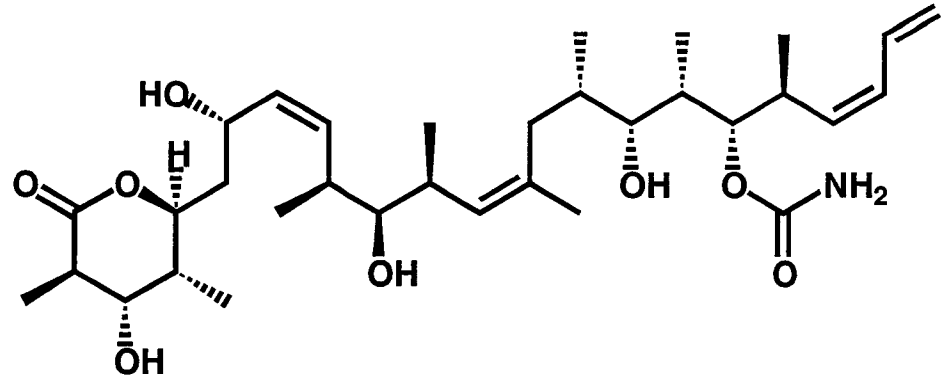
John Baird

July 6, 2004

Isolation and Properties



X-Ray Structure to determine relative Stereochemistry



First isolated in 1990 from *Discodermia dissoluta*

Collected at a depth of 33m to provide 0.002% w/w from the frozen sponge

Solid white crystal with formula $C_{33}H_{55}NO_8$

mp 117-120 ^{0}C; $[\alpha]_D^{23}$ +18

mw 616.38 g/mol

Freemantle, M. *Chem. Eng. News* **2004**, *9*, 33

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

Biological Properties of (+) Discodermolide

One of the most potent anti-cancer agents known

Found to have cytotoxicity in a variety of different human cell lines 3-80 nM

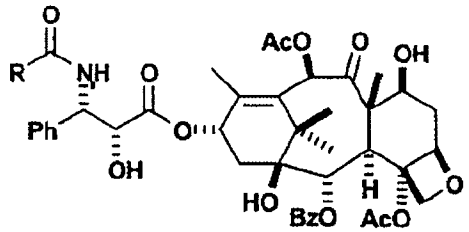
Microtubulin-stabilizing agent; causes cell cycle arrest and cell death

Shows toxicity towards Taxol-resistant cancer cell lines

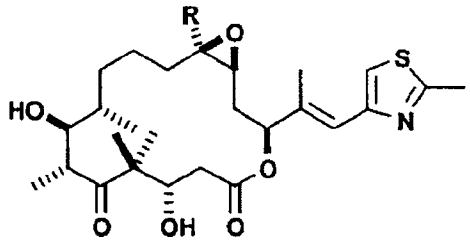
Has been shown to exert a synergistic effect with other anti-cancer drugs

Attempts at isolating an organism for fermentation of discodermolide have failed

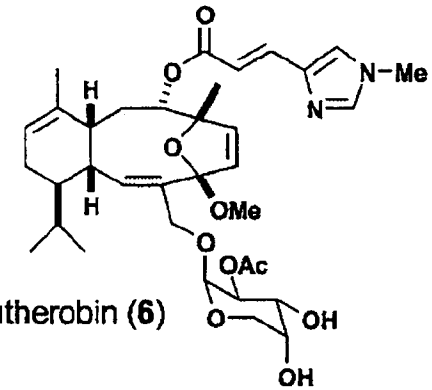
Other Potent anti-cancer agents



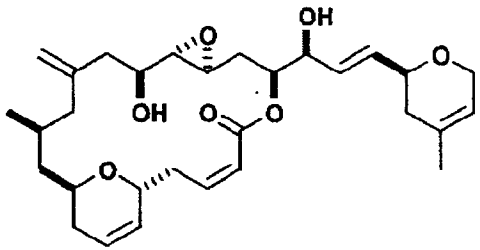
R = Ph : Taxol® (2)
R = OtBu : Taxotere® (11)



R = H : epothilone A (3)
R = Me : epothilone B (4)



eleutherobin (6)



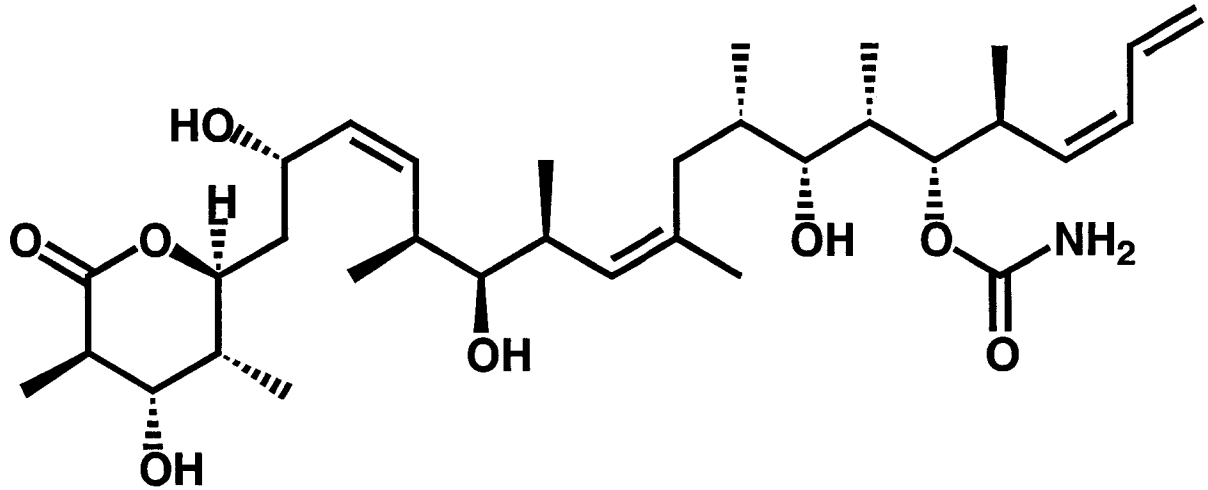
laulimalide (7)

Freemantle, M. *Chem. Eng. News* **2004**, *9*, 33

Smith, A. B. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 8654

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

Key Synthetic Challenges



Molecule possesses:
13 stereocenters

A trisubstituted olefin

3 Z-configured alkenes, one part of a terminal diene

A functionalized δ-lactone, and carbamate moeities

Must prepare using high-yielding, efficient steps!!!

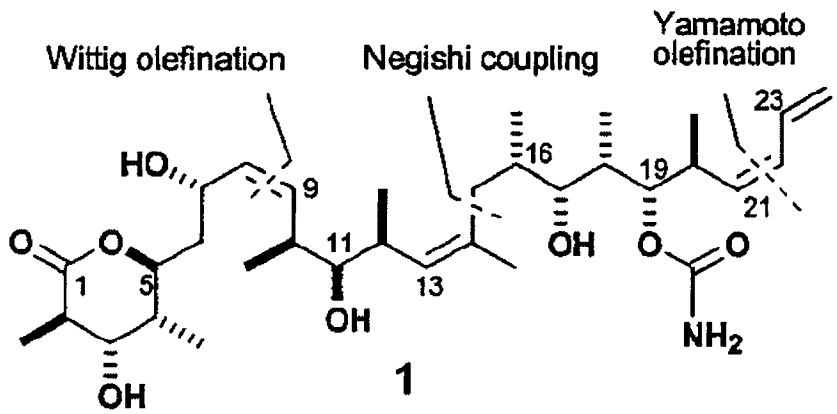
Previous Syntheses

First by Schreiber, made *ent*-discodermolide in 1993,
and later reported the natural antipode in 1996.

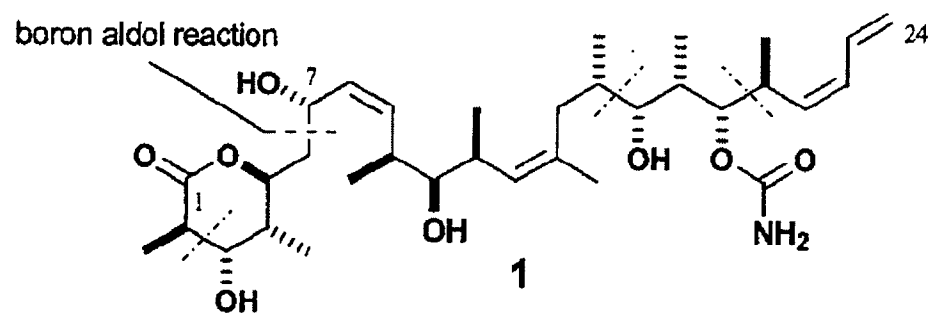
Synthesis of *ent* by Smith in 1995, later synthesized natural antipode

Other syntheses by Patterson, Myles, Marshall

Smith General Retrosynthesis



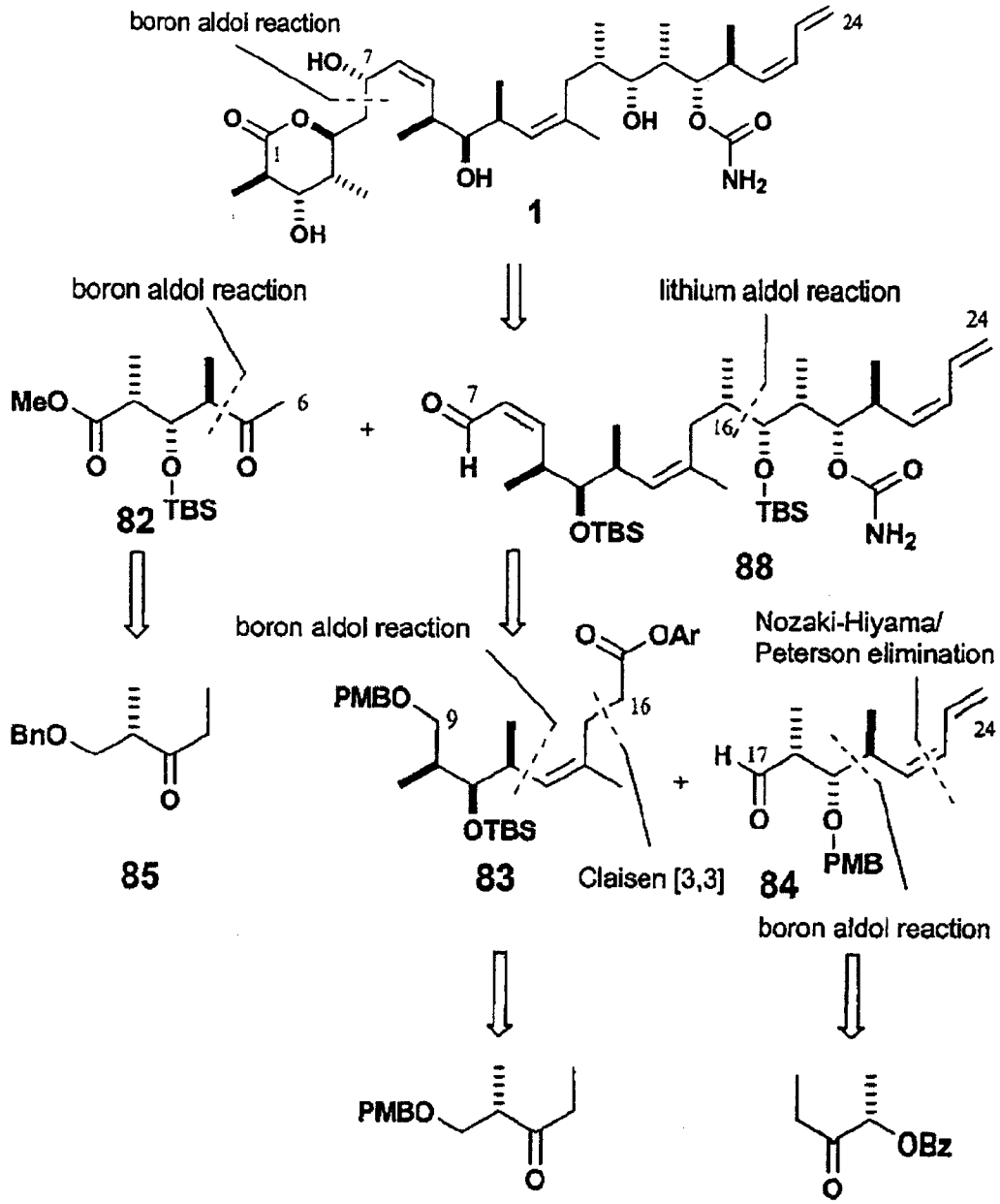
Patterson General Retrosynthesis



Novartis Industrial Synthesis is a hybrid of Smith and Patterson syntheses

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

Paterson Retrosynthesis



Purchase

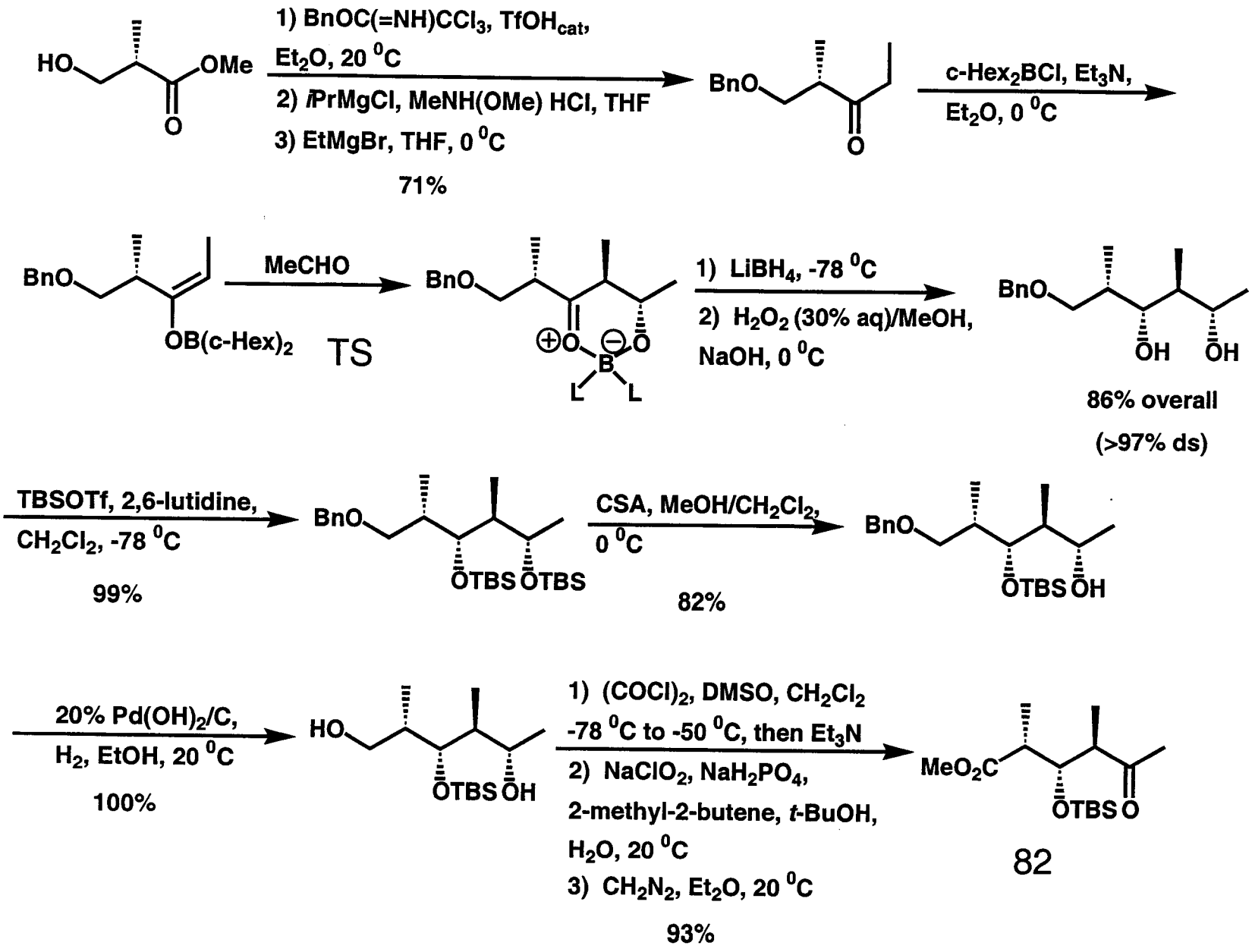
3 chiral centers

Install

8 chiral centers with B

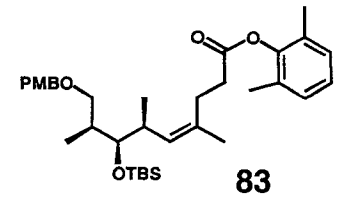
2 chiral centers with Li

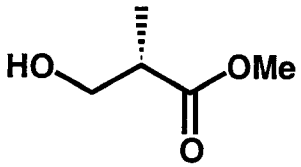
Preparation of 82



Paterson, I. et. al. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

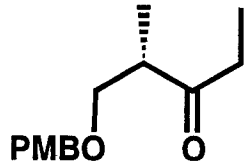
Preparation of 83





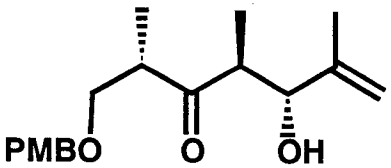
1) $PMBOC(=NH)CCl_3$, $TfOH_{cat}$, Et_2O, 20 °C
2) *i*PrMgCl, MeNH(OMe) HCl, THF
3) EtMgBr, THF, 0 °C

77%



1) c-Hex_2BCl, Et_3N, Et_2O
$H_2C=C(Me)CHO$
-78 to -20 °C
2) H_2O_2 (30% aq)/MeOH, pH 7 buffer, 0 °C

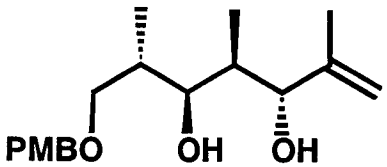
95%



(>97% ds)

$Me_4NBH(OAc)_3$, MeCN/AcOH

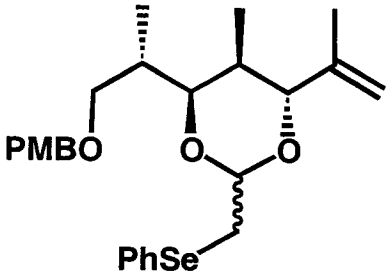
94%



(>97% ds)

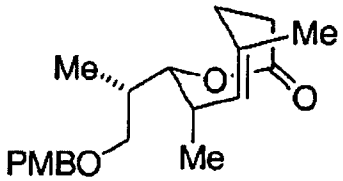
$PhSeCH_2CH(OEt)_2$, toluene, $PPTs_{cat}$, reflux

94%

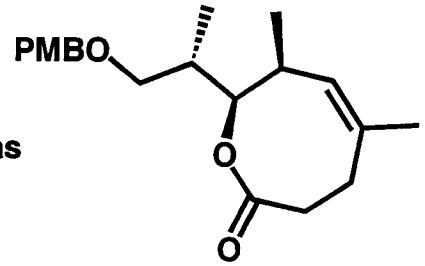


1) $NaIO_4$, $NaHCO_3$, $MeOH/H_2O$, 20 °C
2) DBU, $H_2C=C(OMe)OTBS$, xylenes, reflux

82%

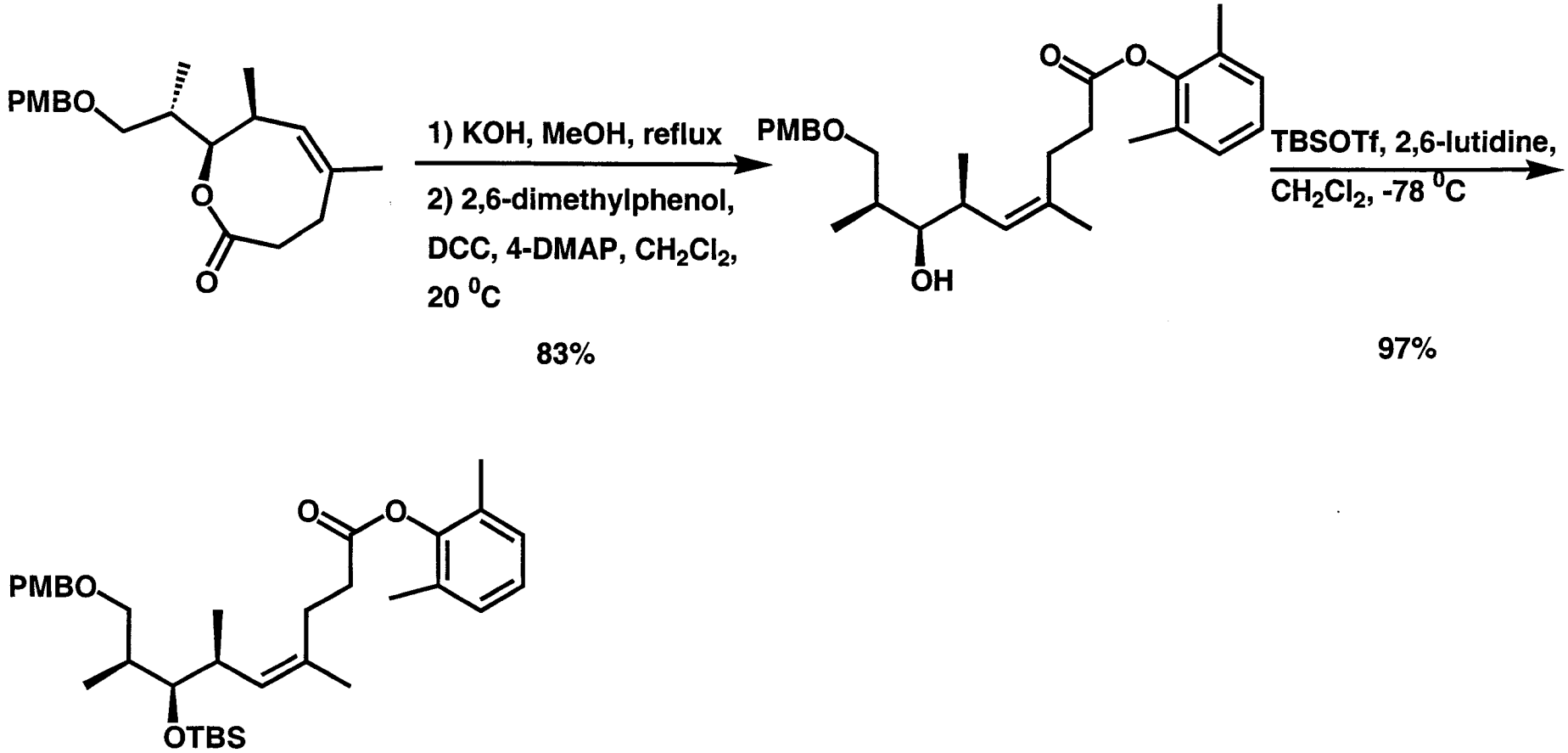


same as



Paterson, I. et. al. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

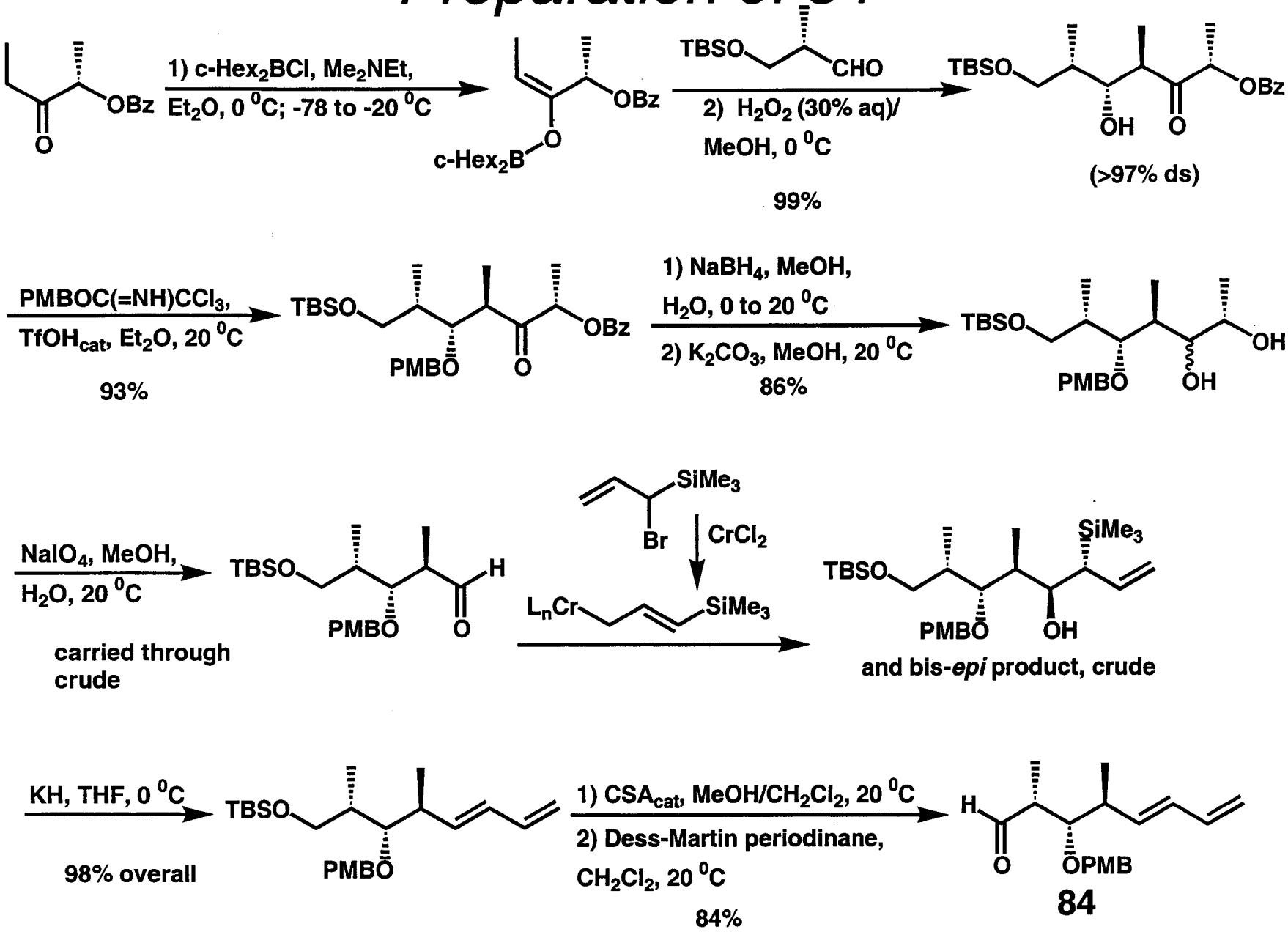
Preparation of 83 continued



83

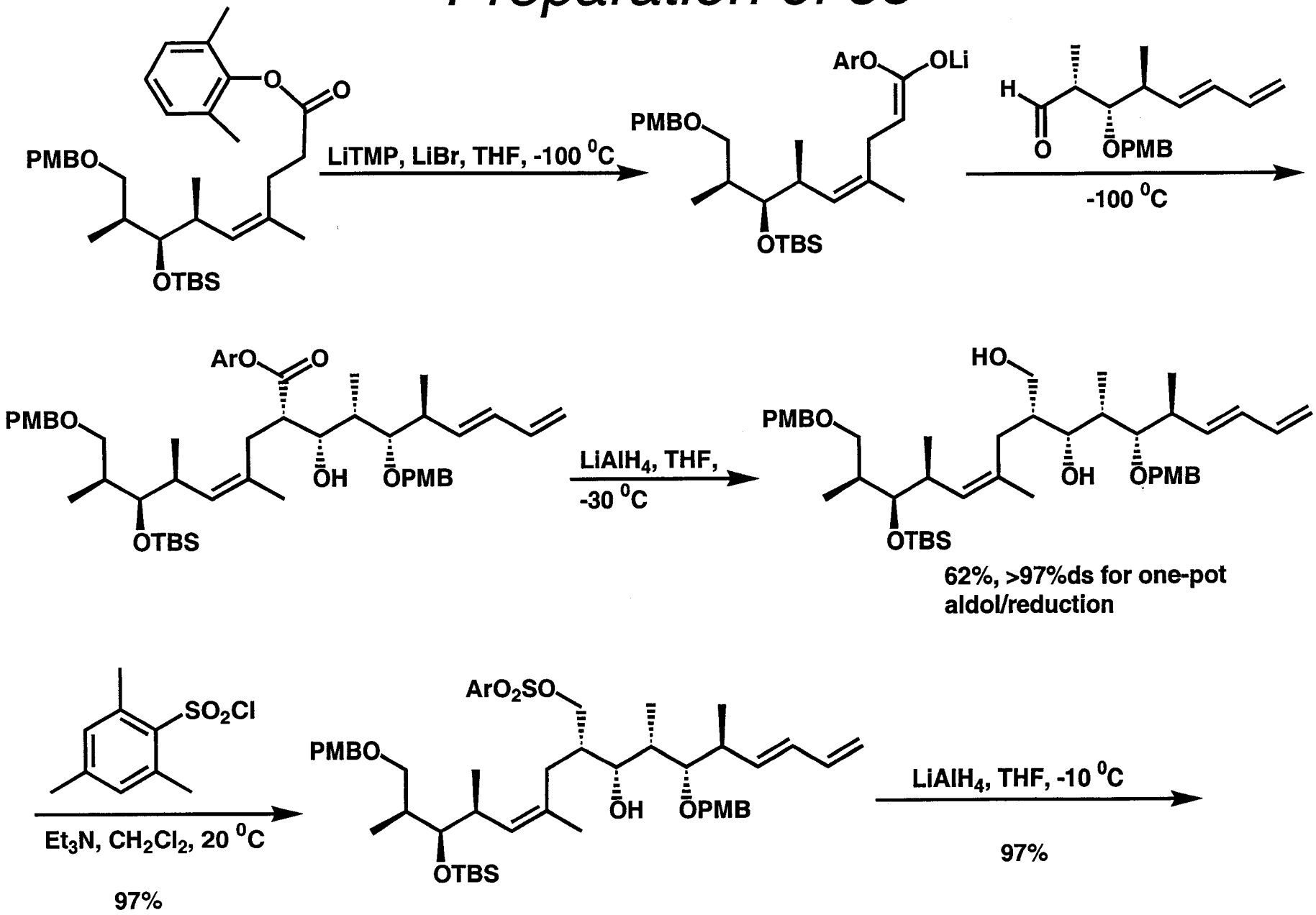
Paterson, I. et. al. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

Preparation of 84



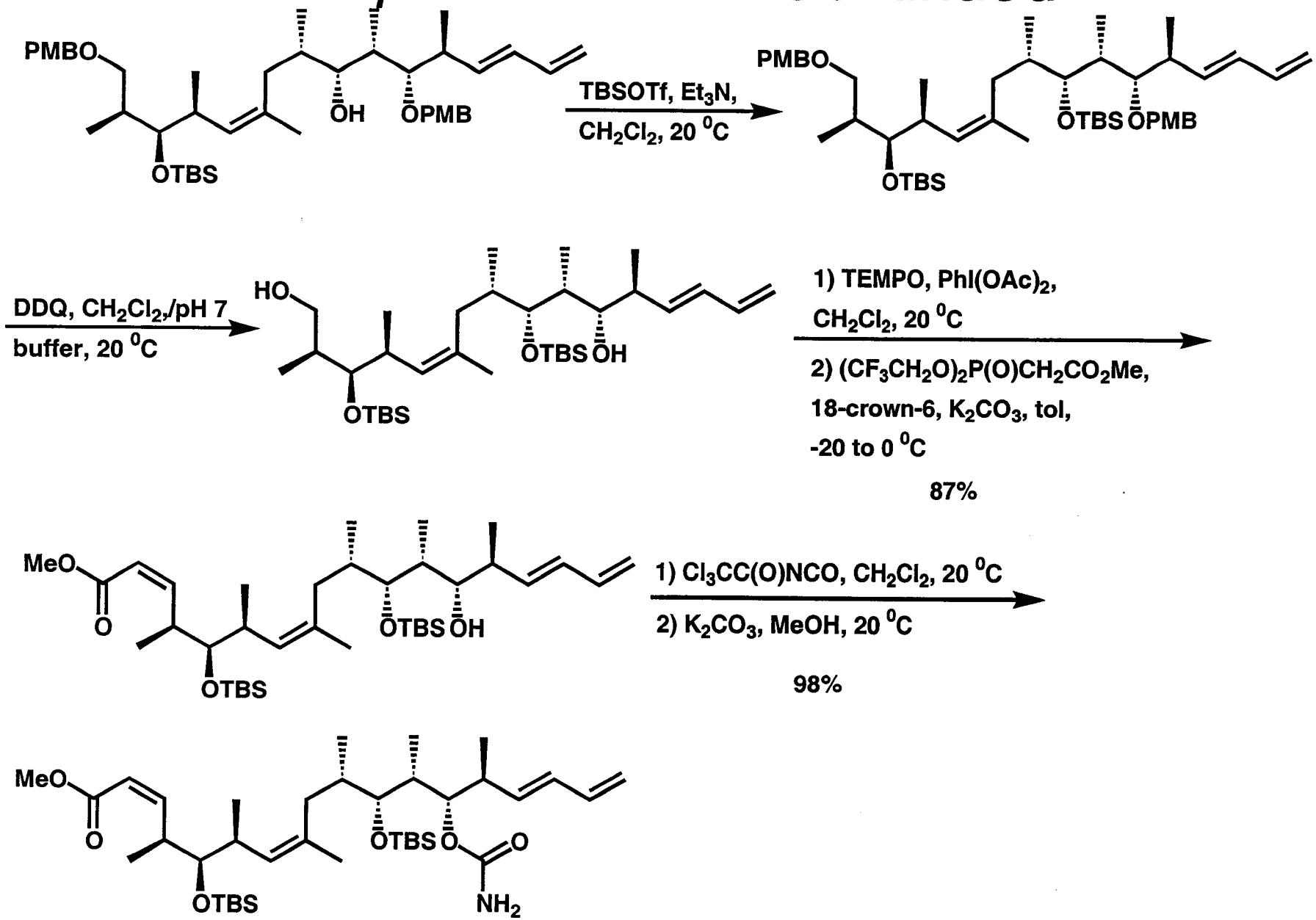
Paterson, I. et. al. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

Preparation of 88



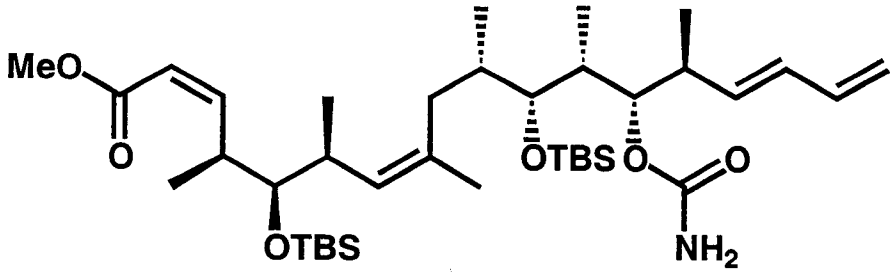
Paterson, I. et. al. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

Preparation of 88 Continued



Paterson, I. et. al. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

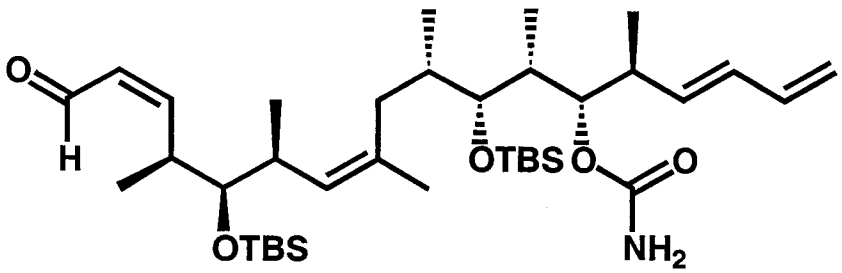
Completion of 88 and Preparation of Boron Enolate



1) DIBAL, CH_2Cl_2, -78 ^{0}C

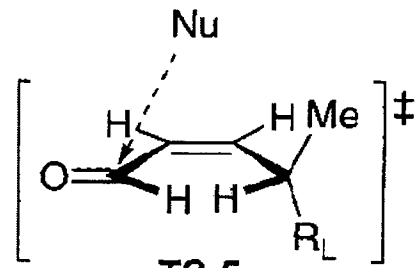
2) Dess-Martin periodinane, CH_2Cl_2, 20 ^{0}C

88%



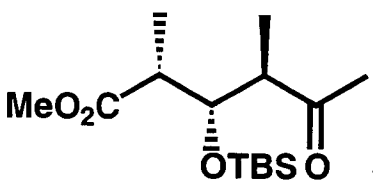
88

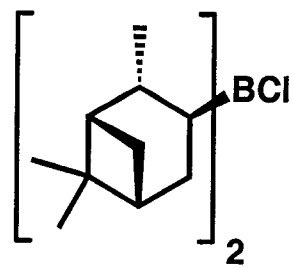
Proposed Rationale



TS-5

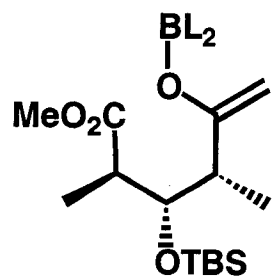
Preparation of Boron Enolate





Et_3N, Et_2O, 0 ^{0}C

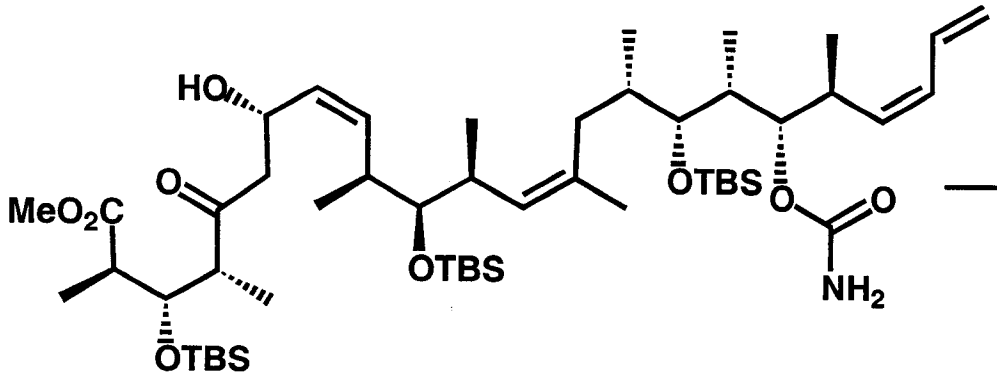
then H_2O_2 (30% aq)/MeOH, 0 ^{0}C



88

Paterson, I. et. al. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

Completion of the Synthesis

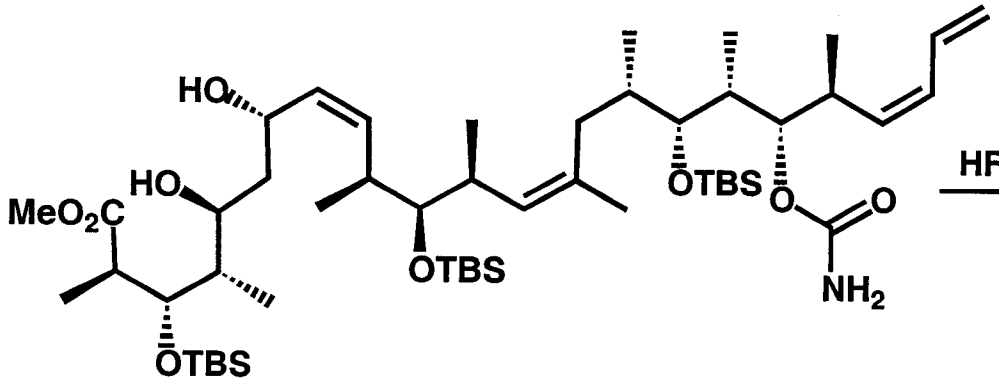


87%, dr 84:16

$Me_4NBH(OAc)_3$

MeCN/AcOH, -20 to 0 ^{0}C

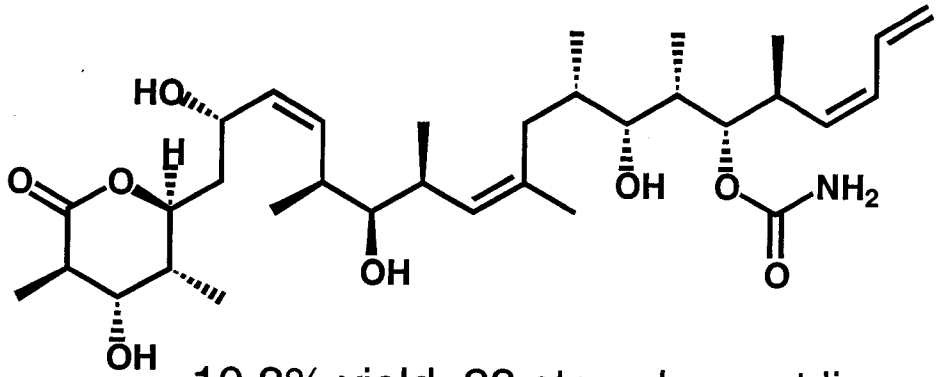
99%



>97% ds

HF•pyr, THF, 20 ^{0}C

85%

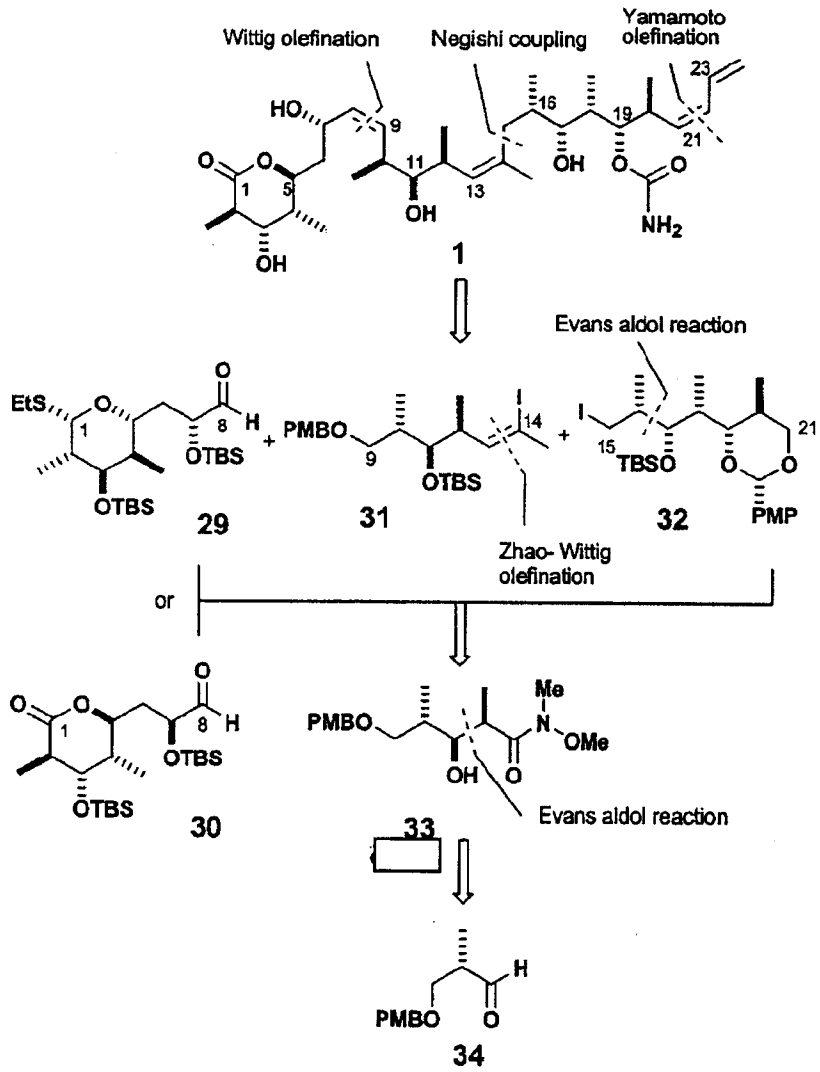


10.3% yield, 23 steps longest linear

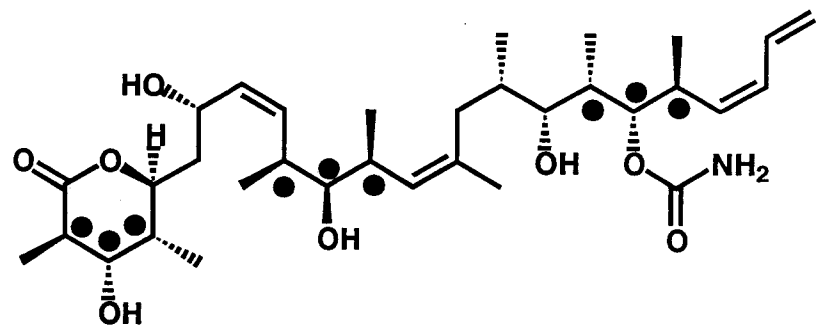
(+)-Discodermolide

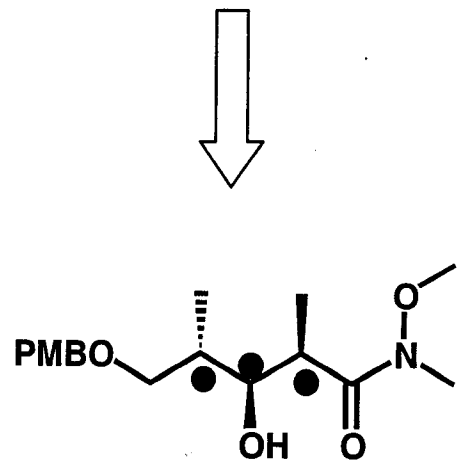
Paterson, I. et. al. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

Smith Synthesis



Takes advantage of repeating Triad of stereocenters

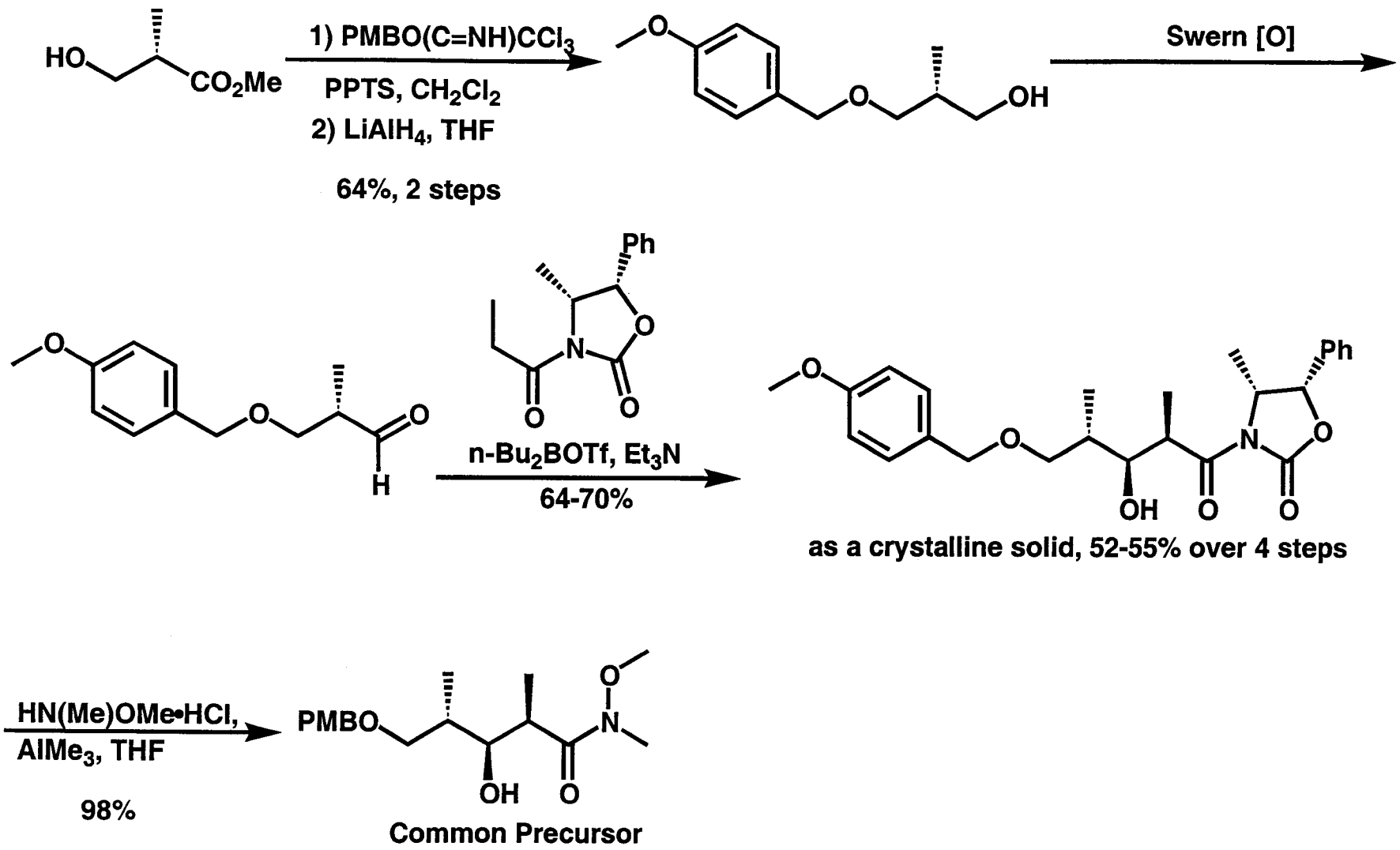




Common Precursor

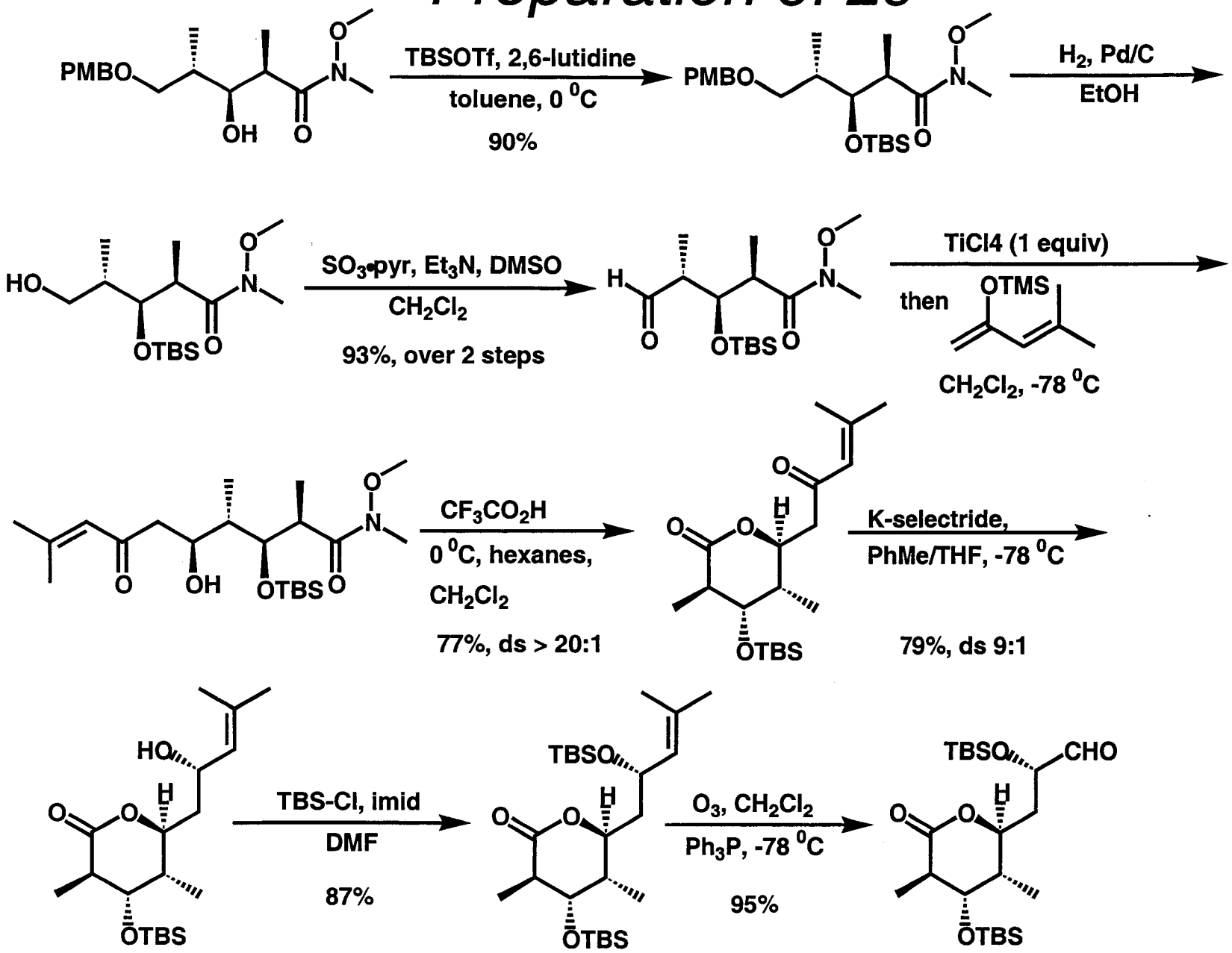
Smith, A. B. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 8654

Preparation of the Common Precursor



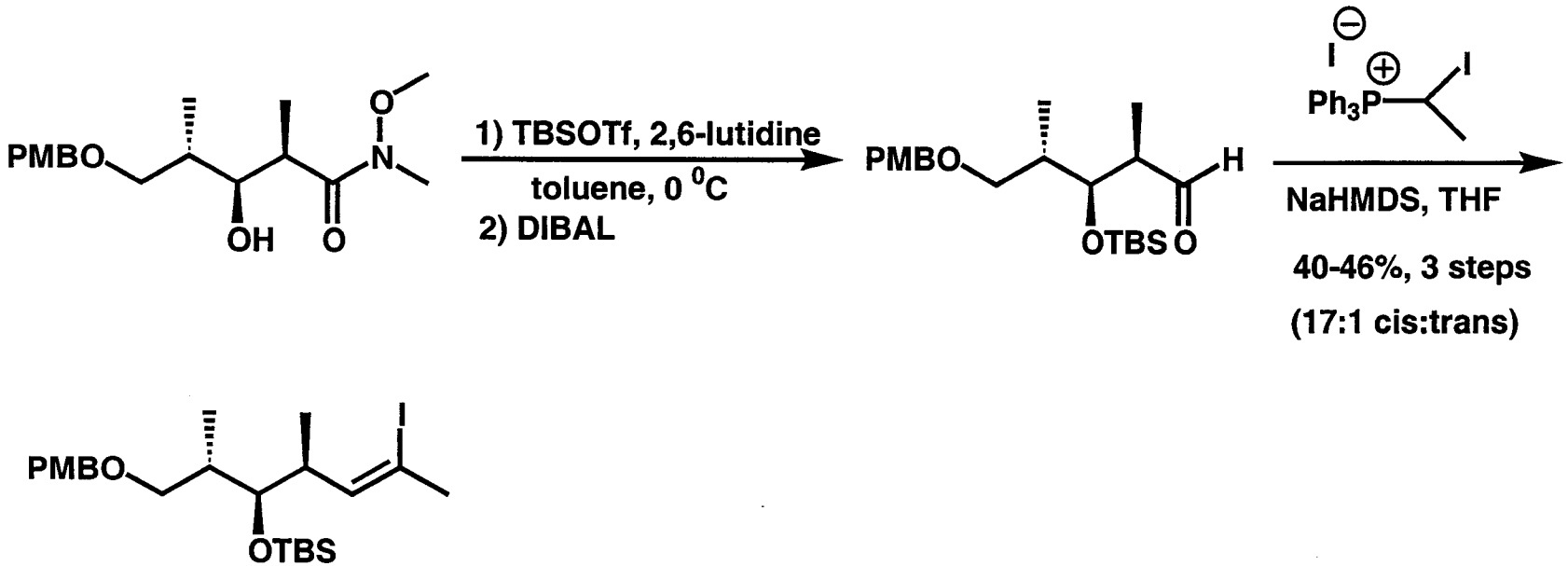
Smith, A. B. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 8654

Preparation of 29



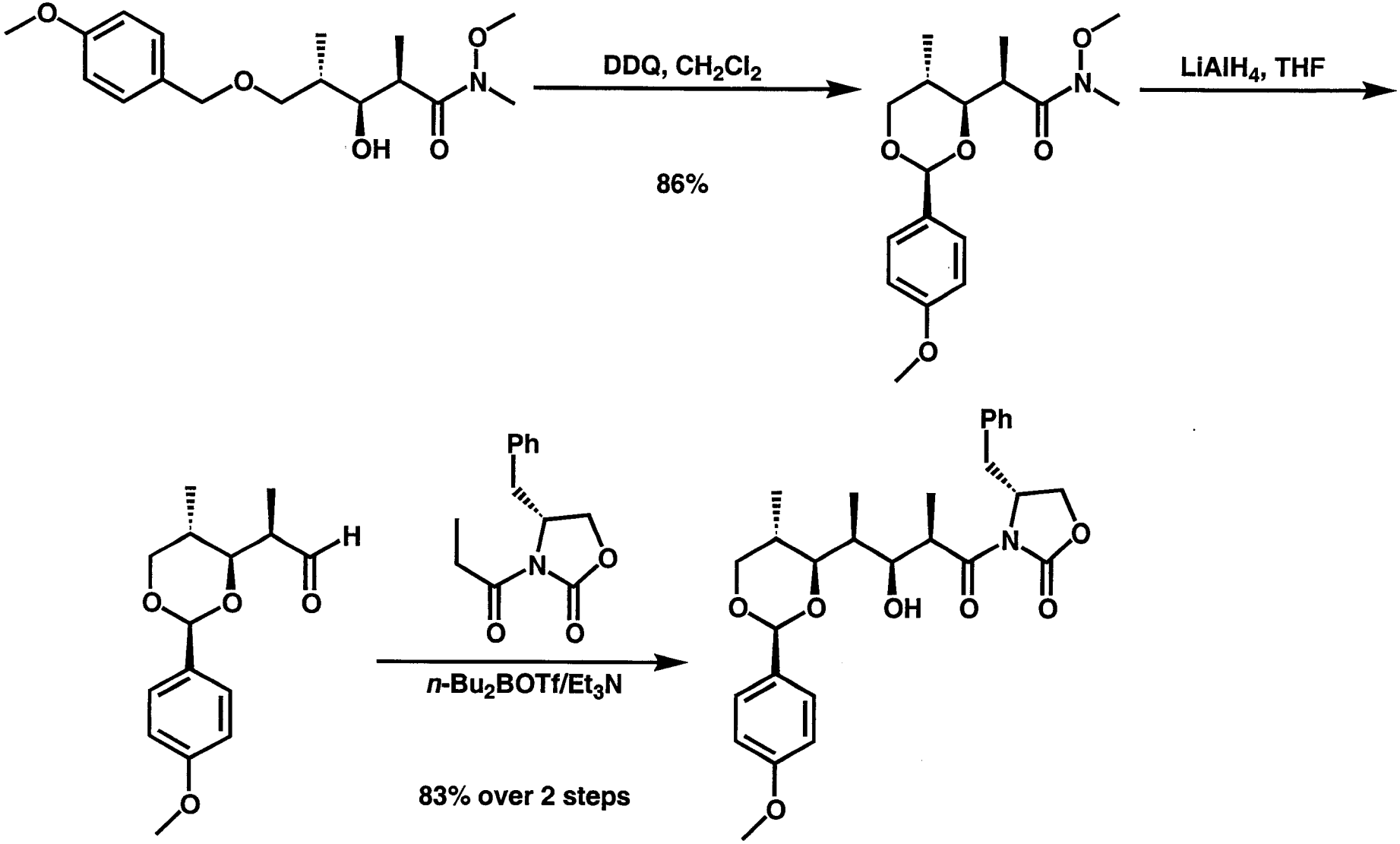
Smith, A. B. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 8654

Preparation of Vinyl Iodide 31



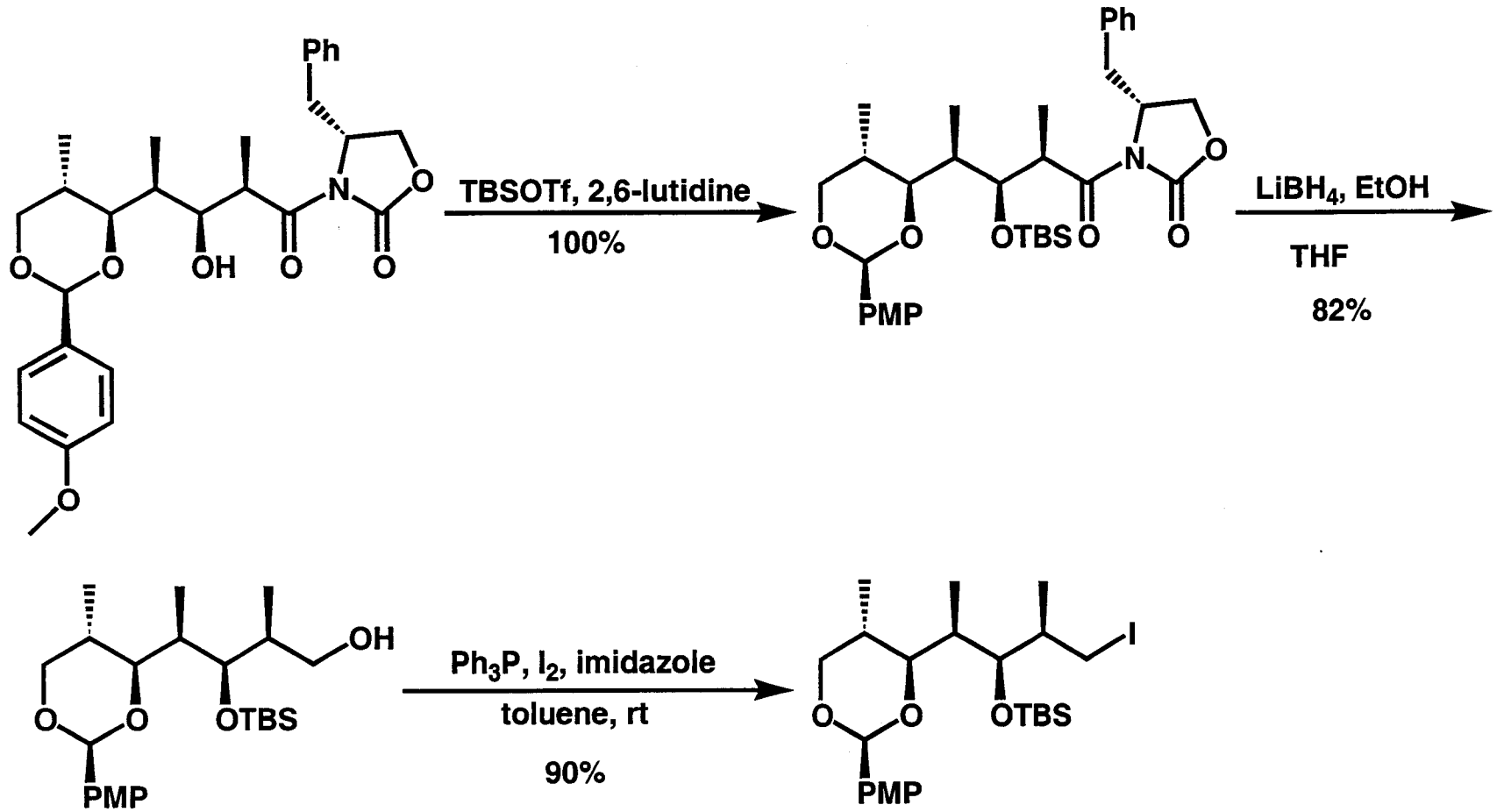
Smith, A. B. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 8654

Preparation of Fragment 32



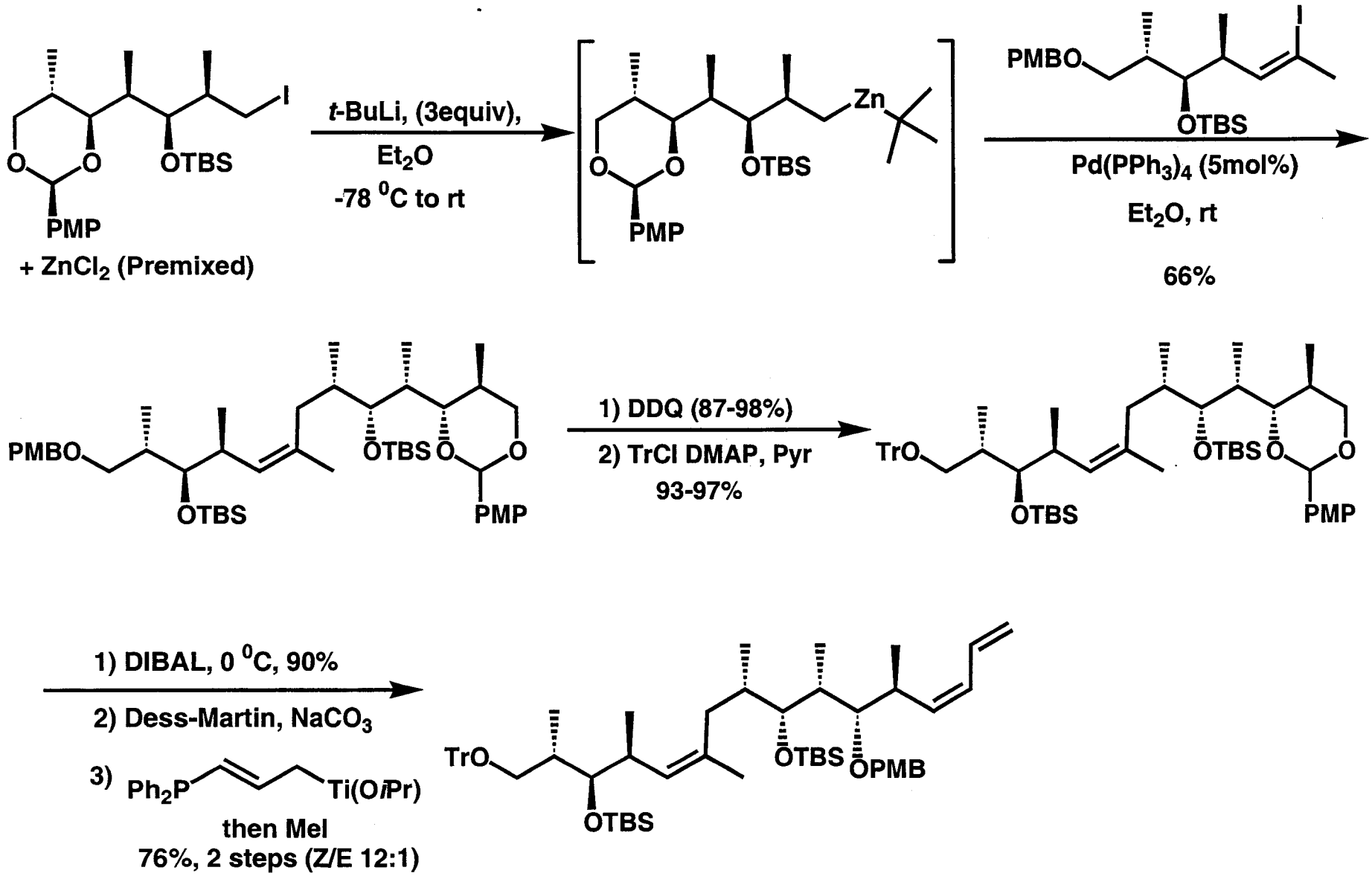
Smith, A. B. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 8654

Preparation of 32 Continued



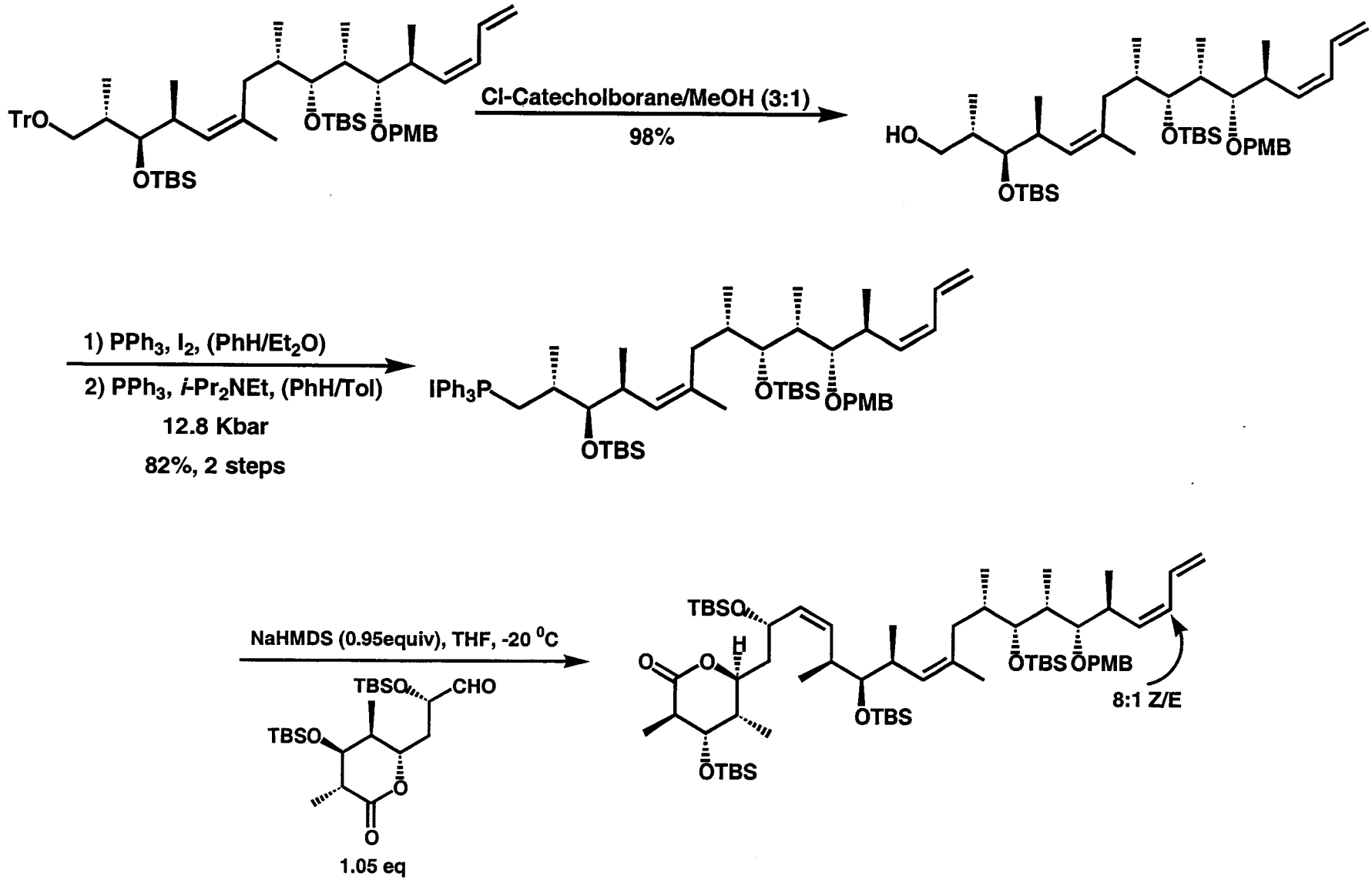
Smith, A. B. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 8654

Coupling 32 with Vinyl Iodide 31



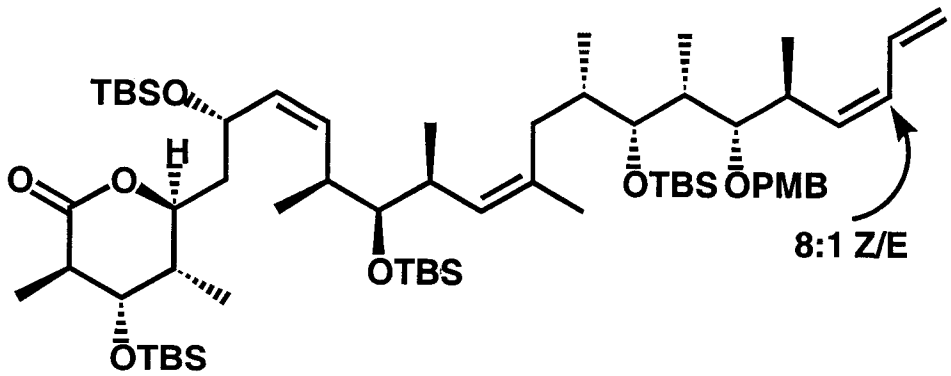
Smith, A. B. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 8654

Wittig Coupling

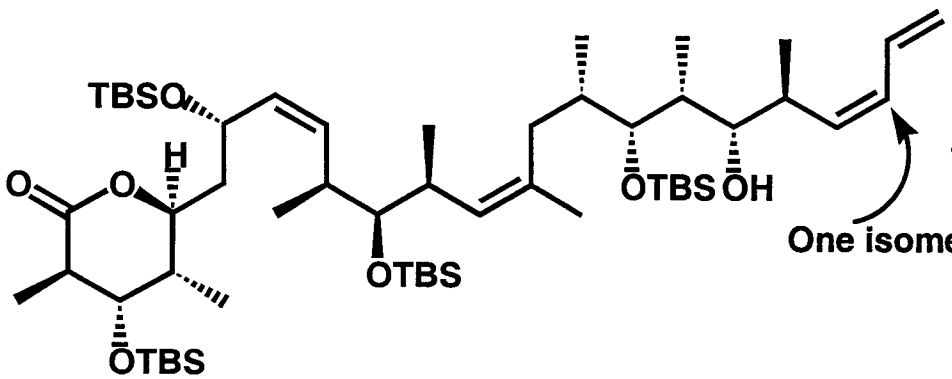


Smith, A. B. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 8654

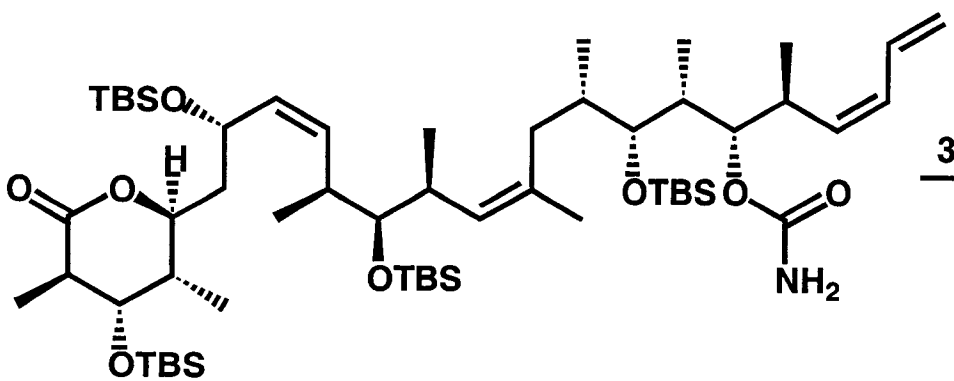
Completion of the Synthesis



$\xrightarrow[\text{87\%, but 98\% based on E/Z purity prior to Wittig}]{\text{DDQ, } CH_2Cl_2, H_2O}$



$\xrightarrow[\text{95\%}]{Cl_3CC(O)NCO;\ Al_2O_3}$



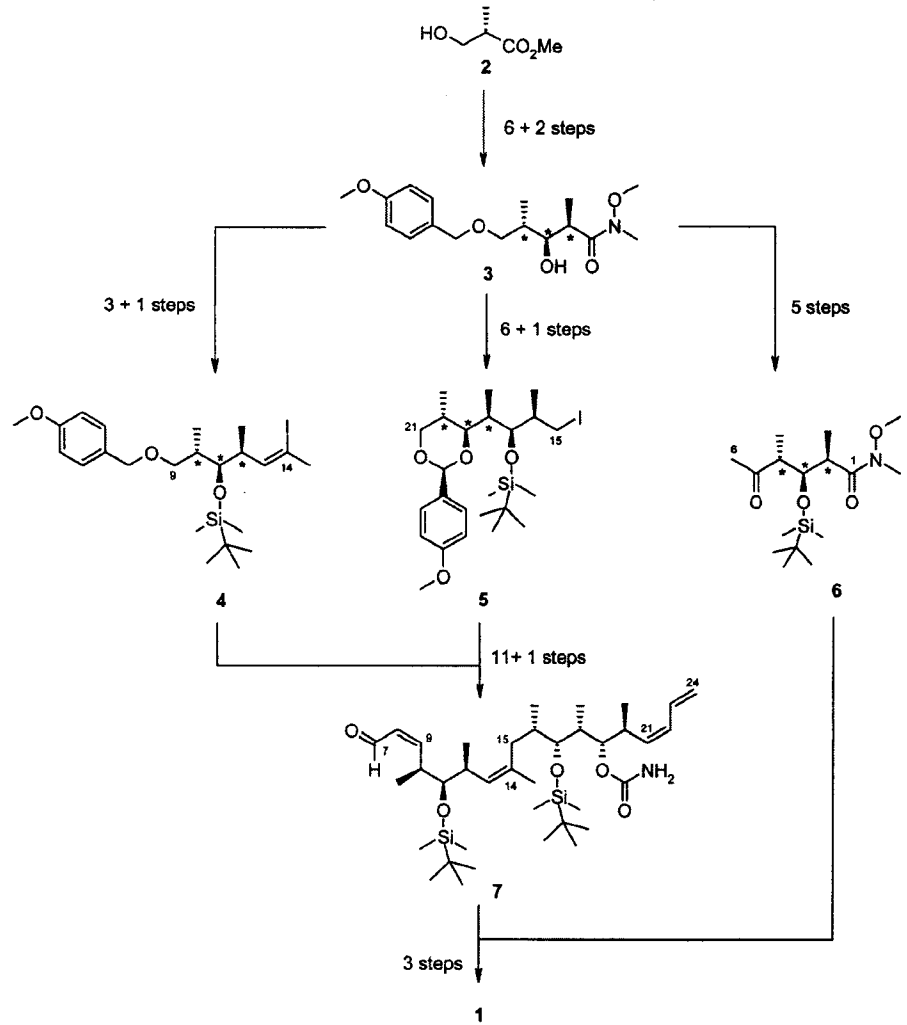
$\xrightarrow[\text{93\%}]{\text{3 N HCl/MeOH, rt}}$ (+) Discodermolide

1.043g, 6% yield
24 steps longest linear

Smith, A. B. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 8654

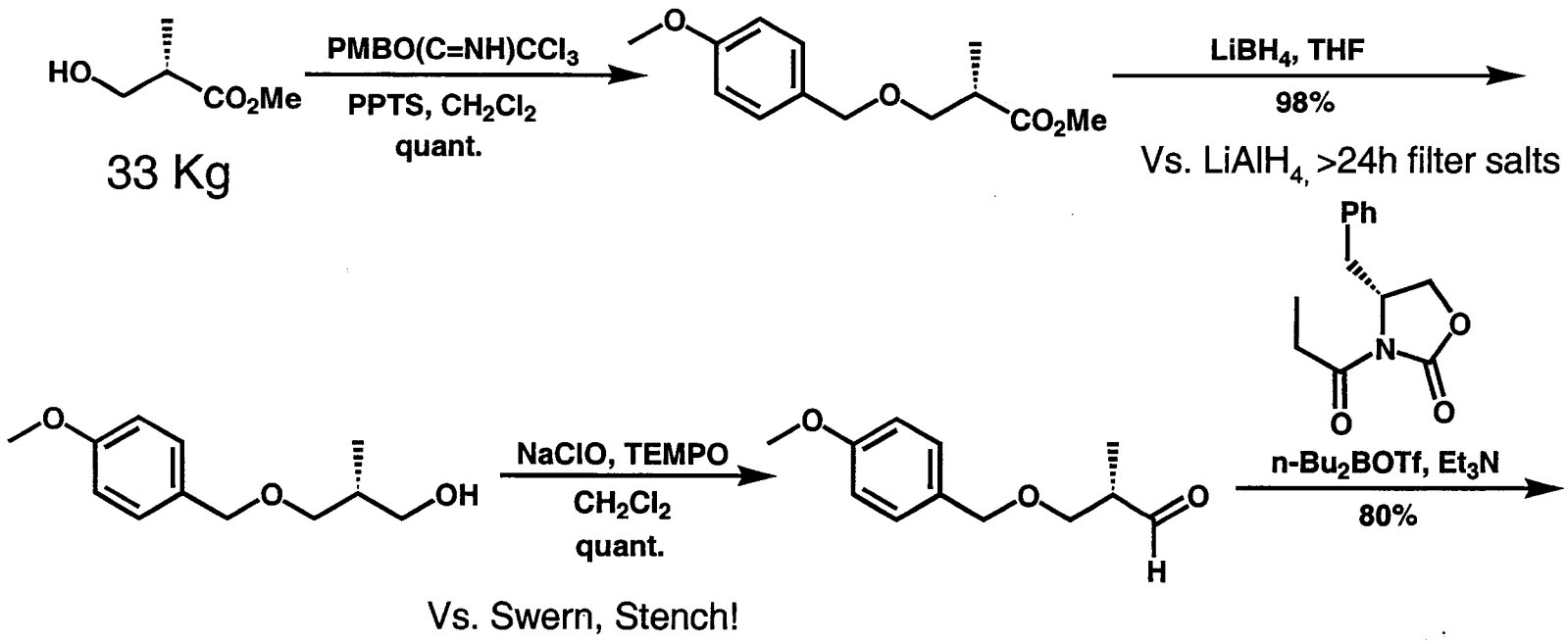
Novartis Synthesis

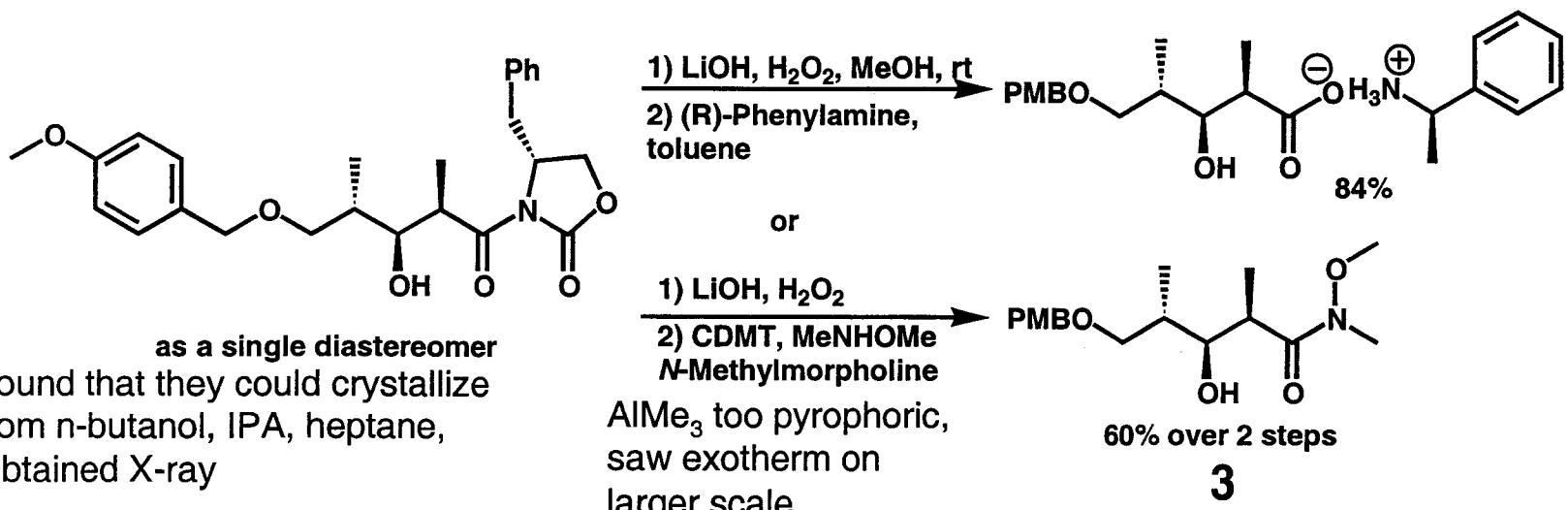
Novartis synthetic route to (+)-discodermolide



Mickel, S.J. et al. *Org. Process Res. Dev.* **2004**, *8*, 92

Preparation of Common Fragment 3





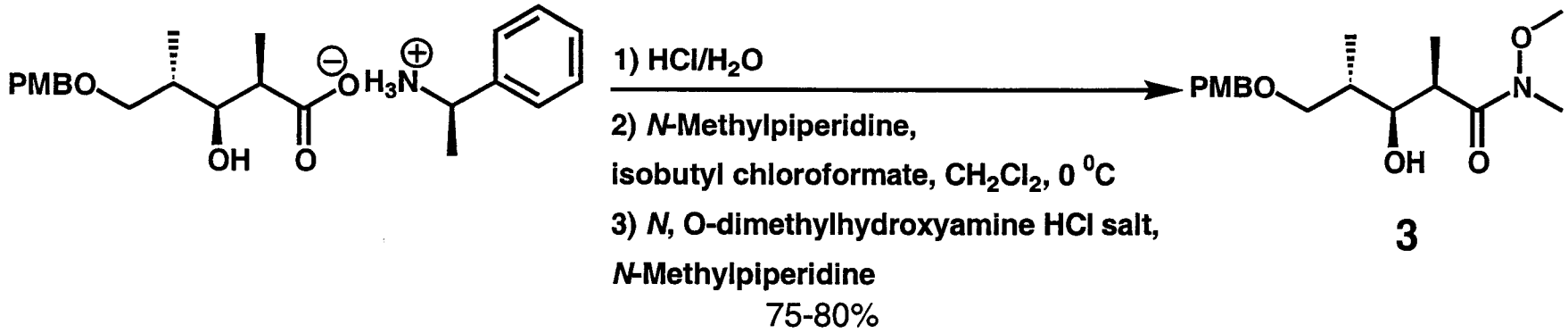
as a single diastereomer

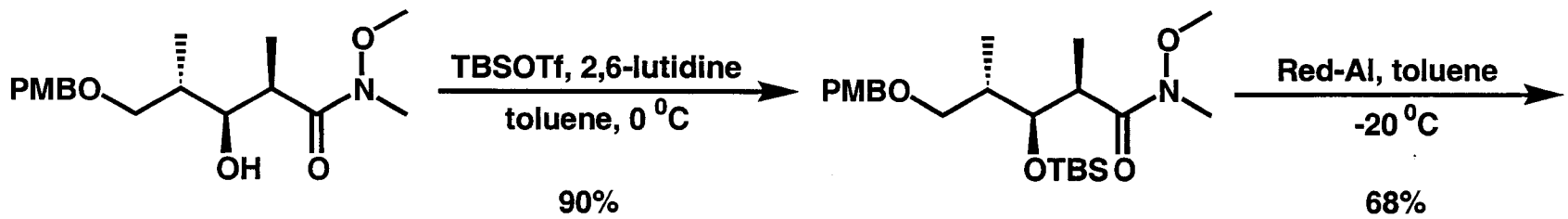
Found that they could crystallize from n-butanol, IPA, heptane, Obtained X-ray

$AlMe_3$ too pyrophoric, saw exotherm on larger scale

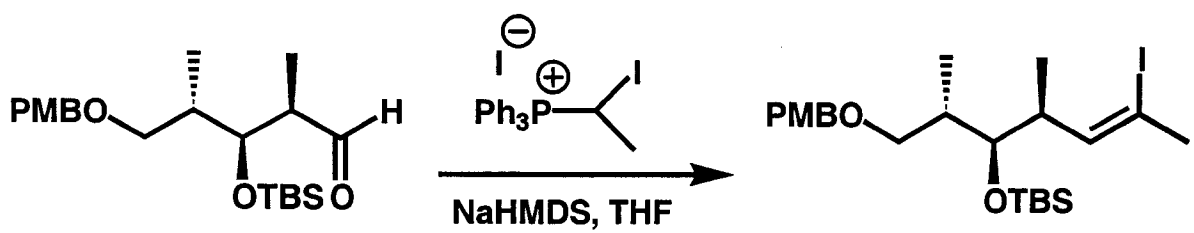
Mickel, S.J. et al. *Org. Process Res. Dev.* **2004**, *8*, 92

Fragment 3 Elaboration to 4





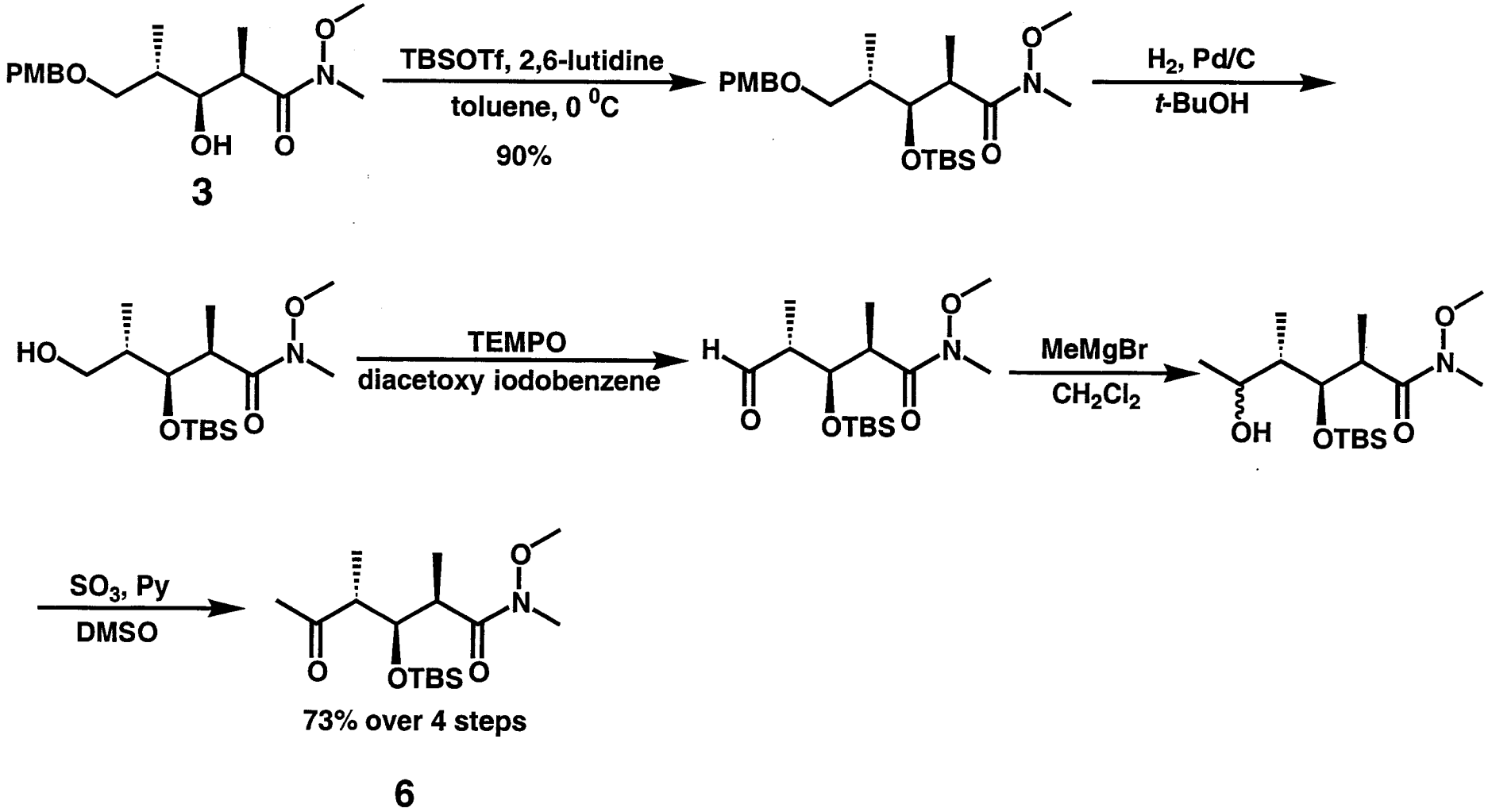
Vs. DIBAL, observed over reduction; -78 °C hard to regulate in pilot plant



Used vinyl iodide/coupling over Patterson's method because of high toxicity of Se

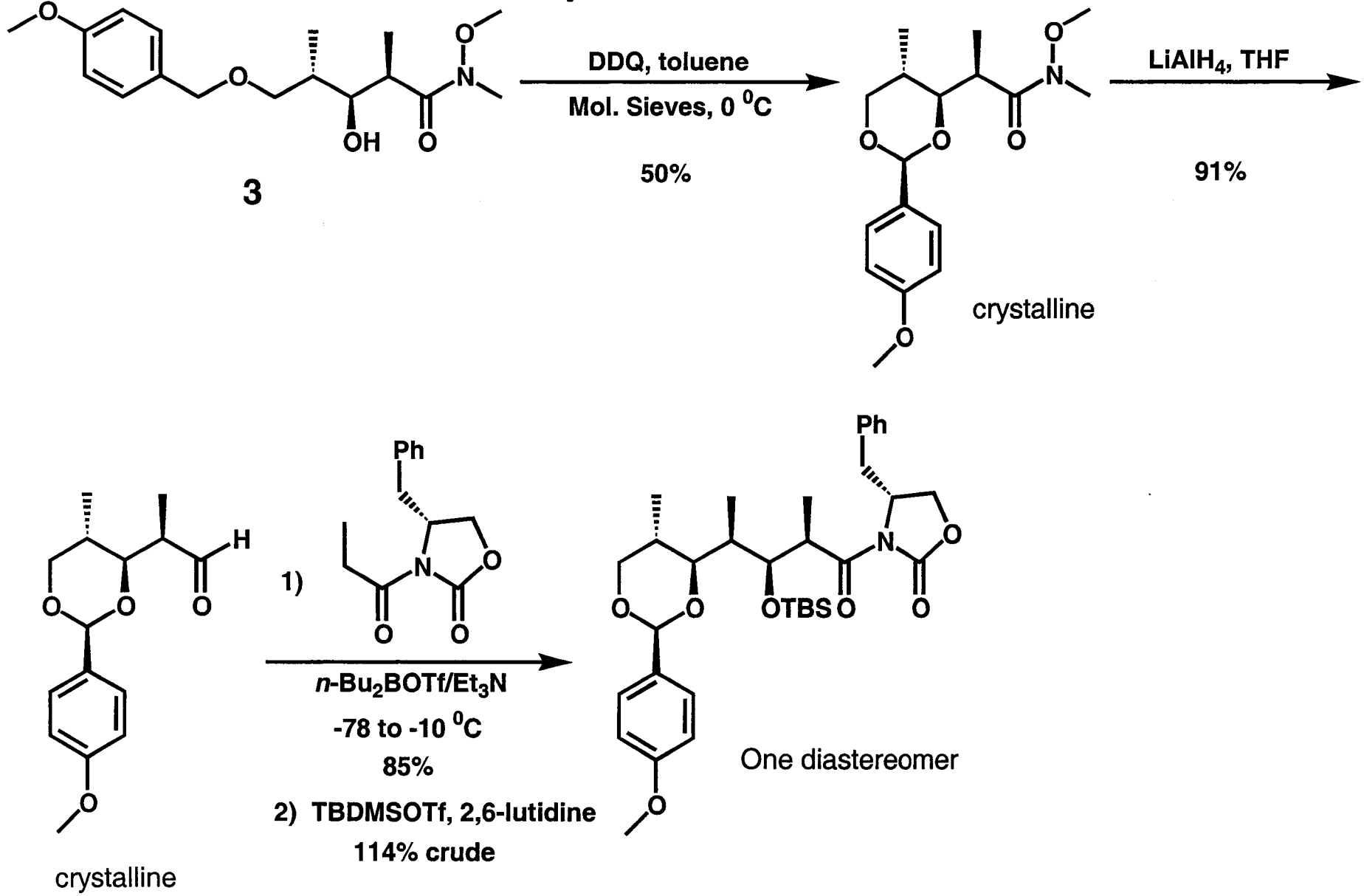
Mickel, S.J. et al. *Org. Process Res. Dev.* **2004**, *8*, 101

Preparation of 6



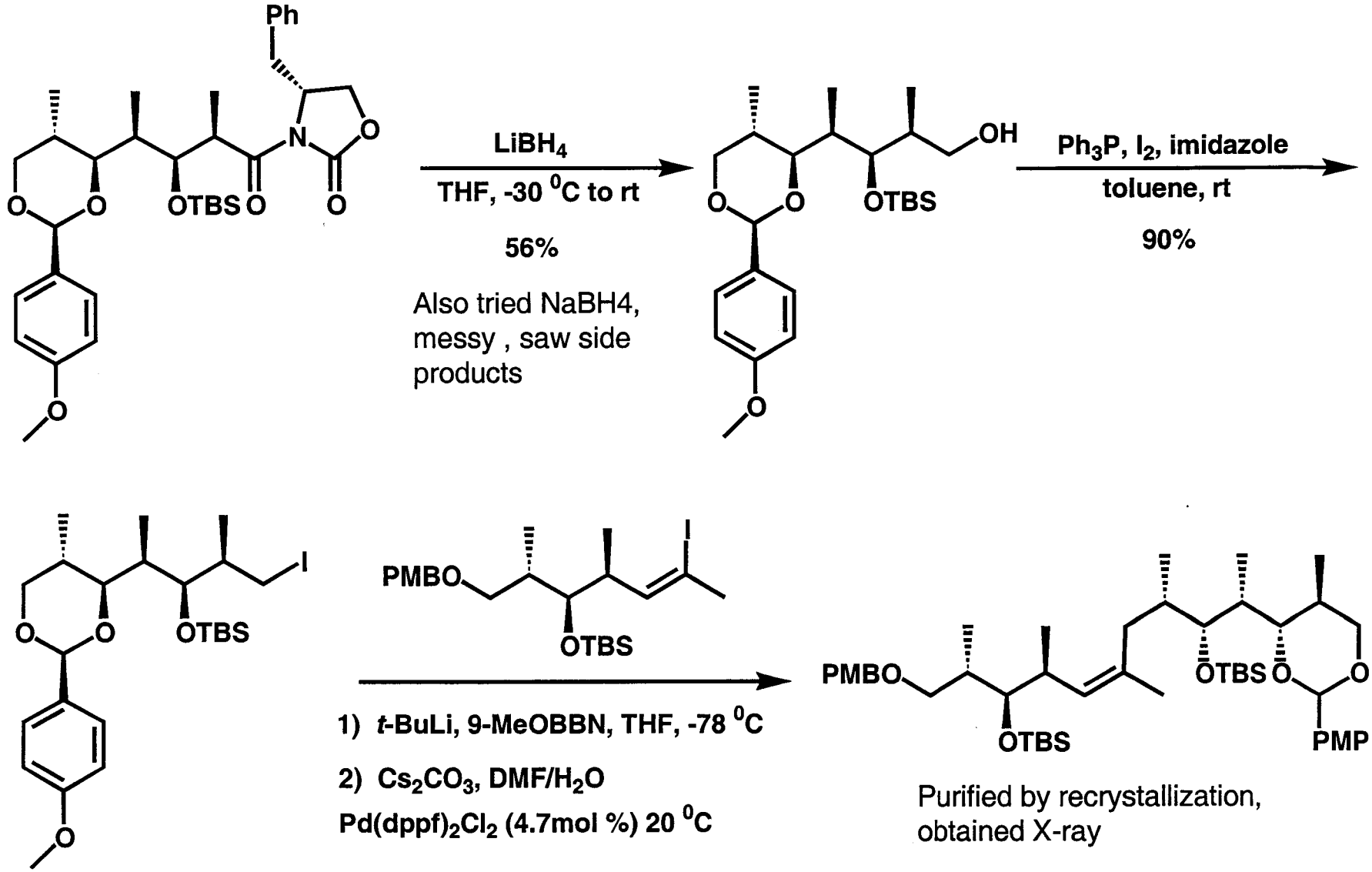
Mickel, S.J. et al. *Org. Process Res. Dev.* **2004**, *8*, 101

Preparation of 5



Mickel, S.J. et al. *Org. Process Res. Dev.* **2004**, *8*, 107

Completion of 5 and Elaboration

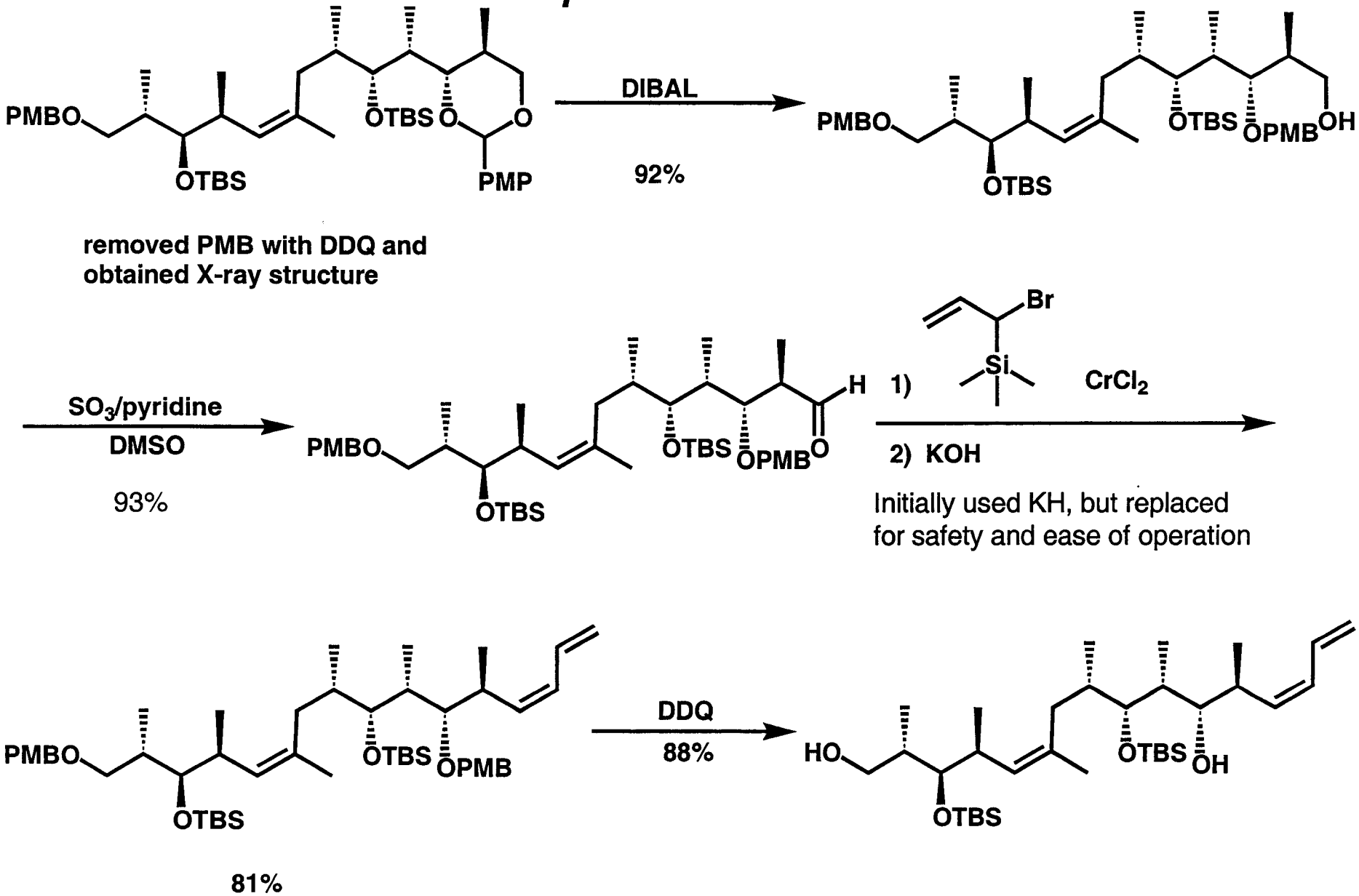


Purified by recrystallization, obtained X-ray

Fragment **5**

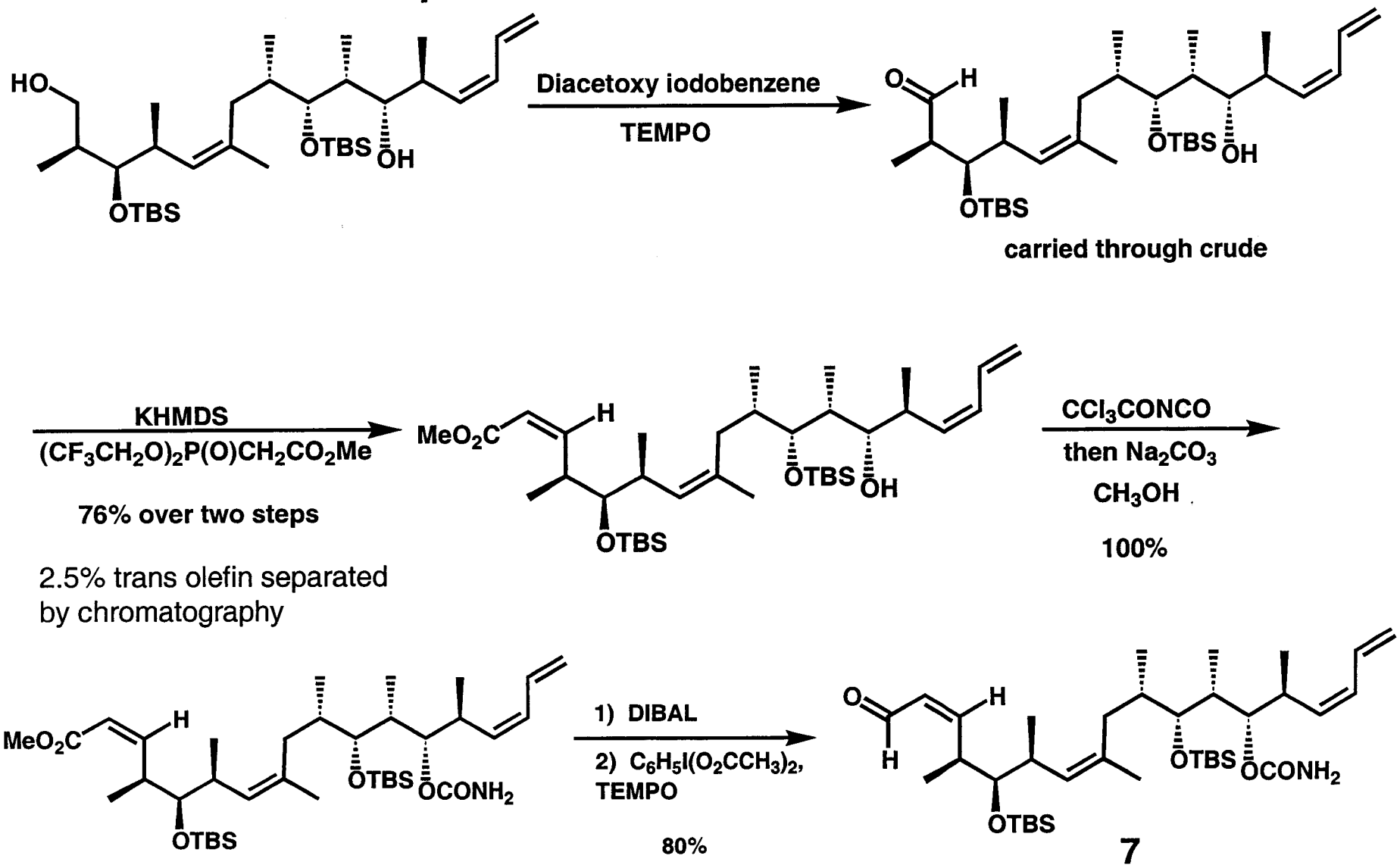
Mickel, S.J. et al. *Org. Process Res. Dev.* **2004**, *8*, 107

Preparation of 7



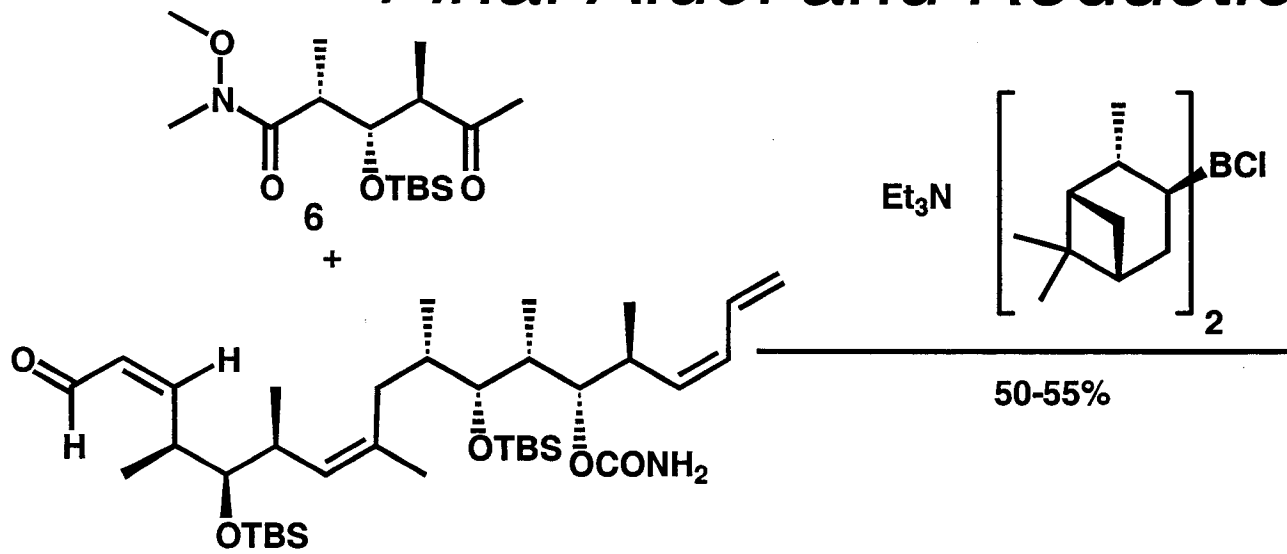
Mickel, S.J. et al. *Org. Process Res. Dev.* **2004**, *8*, 113

Preparation of 7 Continued



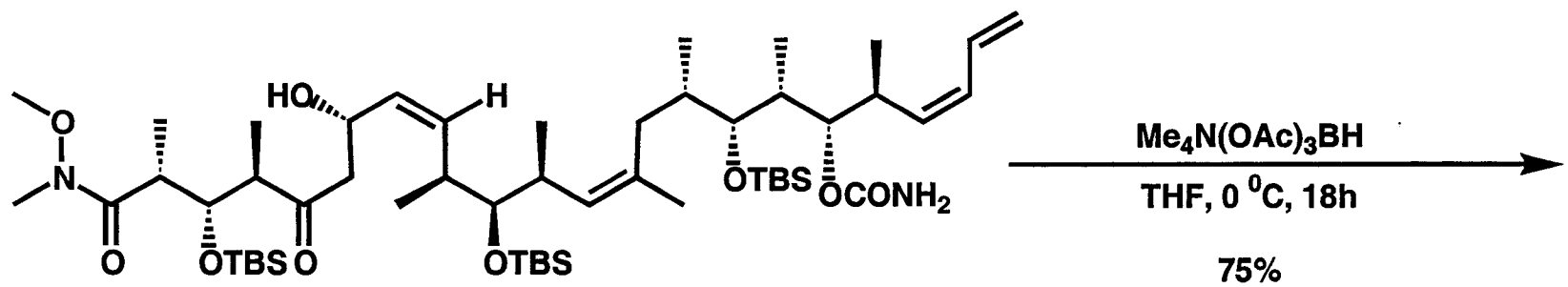
Mickel, S.J. et al. *Org. Process Res. Dev.* **2004**, *8*, 113

Final Aldol and Reduction



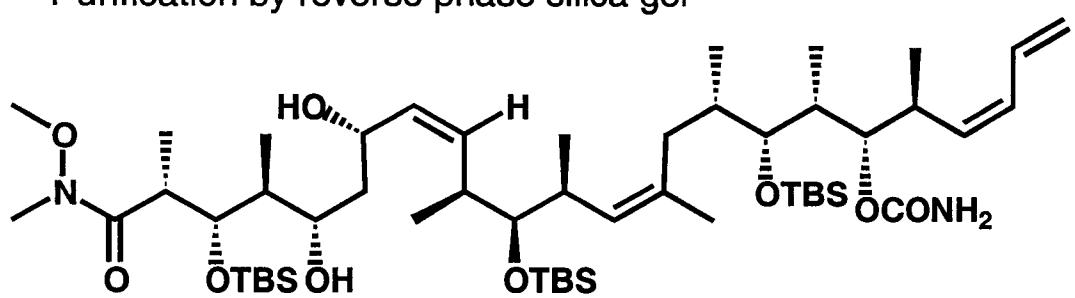
Handling of solid Ipc borane was problematic; hygroscopic and decomposed on storage

Problem solved by using it as a solution in hexane



4:1 diastereoselectivty

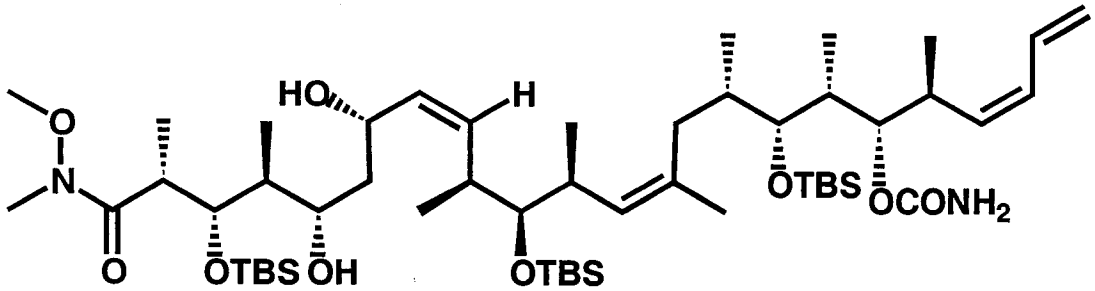
Purification by reverse phase silica gel



Noted "high stereoselectivity"

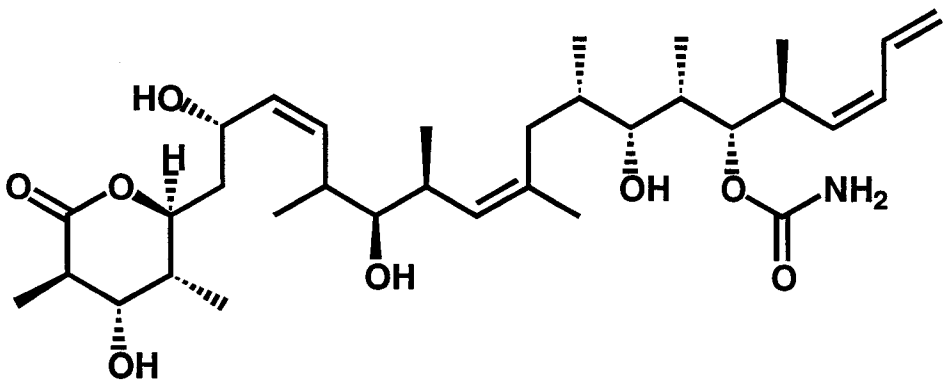
Mickel, S.J. et al. *Org. Process Res. Dev.* **2004**, *8*, 122

Completion of the Synthesis…



HCl/ MeOH

70%



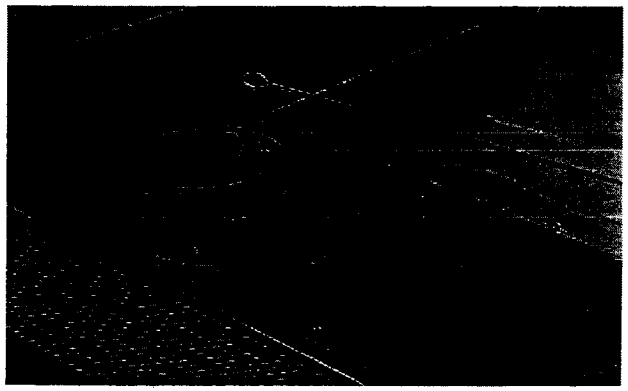
(+)-Discodermolide

61.7 g

39 steps (26 steps longest linear)

17 large scale chromatographic purifications

0.65% yield



Mickel, S.J. et al. *Org. Process Res. Dev.* **2004**, *8*, 122

Conclusions

Paterson Synthesis-
Showcases Boron-mediated aldol reactions
Claisen used to synthesize trisubstituted olefin
Nozaki-Hiyama/Peterson Olefination
10.3% yield; 23 steps longest-linear

Smith Synthesis-
Takes advantage of repeating stereochemical triad to use common fragment
Uses Evans aldol reactions
Negishi Cross-coupling to synthesize trisubstituted olefin
Yamamoto Olefination to access diene
6% yield; 24 steps longest-linear
Synthesized 1.043 g of material

Novartis Synthesis-
Hybrid approach using early steps of Smith Synthesis, and endgame of Paterson
Suzuki-type Cross-coupling to synthesize trisubstituted olefin
Nozaki-Hiyama/Peterson Olefination
0.65% yield; 26 steps longest-linear
Synthesized 61.7 g of material