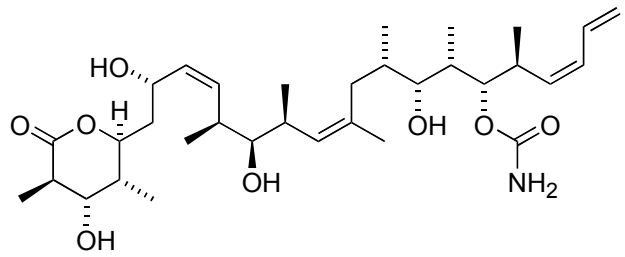
Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide



Organic Process Research & Development **2004**, *8*, 92–100

Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 1: Synthetic Strategy and Preparation of a Common Precursor

Stuart J. Mickel,* Gottfried H. Sedelmeier, Daniel Niederer, Robert Daeffler, Adnan Osmani, Klaus Schreiner, Manuela Seeger-Weibel, Brigitte Bérod, Karl Schaer, and Remo Gamboni

Chemical and Analytical Development, Novartis Pharma AG, CH 4002 Basel, Switzerland

Stephen Chen, Weichun Chen, Christopher T. Jagoe, Frederick R. Kinder, Jr., Mauricio Loo, Kapa Prasad, Oljan Repič, Wen-Chung Shieh, Run-Ming Wang, Liladhar Waykole, David D. Xu, and Song Xue

Novartis Institutes for Biomedical Research, One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

Organic Process Research & Development **2004**, *8*, 101–106

Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 2: Synthesis of Fragments C_{1-6} and C_{9-14}

Stuart J. Mickel,* Gottfried H. Sedelmeier, Daniel Niederer, Friedrich Schuerch, Dominique Grimler, Guido Koch, Robert Daeffler, Adnan Osmani, Alfred Hirni, Karl Schaer, and Remo Gamboni

Chemical and Analytical Development, Novartis Pharma AG, CH 4002 Basel, Switzerland

Andrew Bach, Apurva Chaudhary, Stephen Chen, Weichun Chen, Bin Hu, Christopher T. Jagoe, Hong-Yong Kim, Frederick R. Kinder, Jr., Yugang Liu, Yansong Lu, Joseph McKenna, Mahavir Prashad, Timothy M. Ramsey, Oljan Repič, Larry Rogers, Wen-Chung Shieh, Run-Ming Wang, and Liladhar Waykole

Novartis Institutes for Biomedical Research, One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

Organic Process Research & Development **2004**, *8*, 107–112

Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 3: Synthesis of Fragment C_{15-21}

Stuart J. Mickel,* Gottfried H. Sedelmeier, Daniel Niederer, Friedrich Schuerch, Guido Koch, E. Kuesters, Robert Daeffler, Adnan Osmani, Manuela Seeger-Weibel, E. Schmid, Alfred Hirni, Karl Schaer, and Remo Gamboni

Chemical and Analytical Development, Novartis Pharma AG, CH 4002 Basel, Switzerland

Andrew Bach, Stephen Chen, Weichun Chen, Peng Geng, Christopher T. Jagoe, Frederick R. Kinder, Jr., George T. Lee, Joseph McKenna, Timothy M. Ramsey, Oljan Repič, Larry Rogers, Wen-Chung Shieh, Run-Ming Wang, and Liladhar Waykole

Novartis Institutes for Biomedical Research, One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

Organic Process Research & Development **2004**, *8*, 113–121

Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 4: Preparation of Fragment C_{7-24}

Stuart J. Mickel,* Gottfried H. Sedelmeier, Daniel Niederer, Friedrich Schuerch, Manuela Seger, Klaus Schreiner, Robert Daeffler, Adnan Osmani, Dominique Bixel, Olivier Loiseleur, Jacques Cercus, Hans Stettler, Karl Schaer, and Remo Gamboni

Chemical and Analytical Development, Novartis Pharma AG, CH 4002 Basel, Switzerland

Andrew Bach, Guang-Pei Chen, Weichun Chen, Peng Geng, George T. Lee, Eric Loeser, Joseph McKenna, Frederick R. Kinder, Jr., Kurt Konigsberger, Kapa Prasad, Timothy M. Ramsey, Noela Reel, Oljan Repič, Larry Rogers, Wen-Chung Shieh, Run-Ming Wang, Liladhar Waykole, and Song Xue

Novartis Institutes for Biomedical Research, One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

Organic Process Research & Development **2004**, *8*, 122–130

Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 5: Linkage of Fragments C_{1-6} and C_{7-24} and Finale

Stuart J. Mickel,* Daniel Niederer, Robert Daeffler, Adnan Osmani, Ernst Kuesters, Emil Schmid, Karl Schaer, and Remo Gamboni

Chemical and Analytical Development, Novartis Pharma AG, CH 4002 Basel, Switzerland

Weichun Chen, Eric Loeser, Frederick R. Kinder, Jr., Kurt Konigsberger, Kapa Prasad, Timothy M. Ramsey, Oljan Repič, and Run-Ming Wang

Novartis Institutes for Biomedical Research, One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

Gordon Florence, Isabelle Lyothier, and Ian Paterson

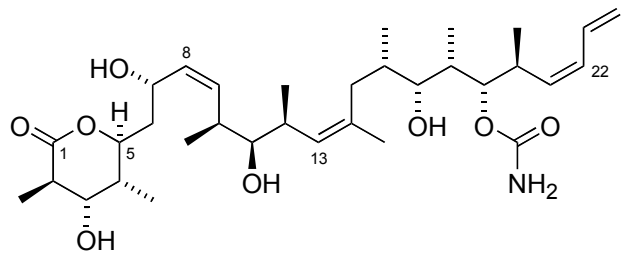
University of Cambridge, Chemical Laboratories Lensfield Road, Cambridge CB2 1EW, UK

Gordon Florence and Ian Paterson

University of Cambridge, Chemical Laboratories Lensfield Road, Cambridge CB2 1EW, UK

- 61.7 g prepared in 39 steps
- 43 chemists worked on the project which lasted 20 months

Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide



- 24 carbon linear polypropionate chain containing 13 stereocenters (6 hydroxyl and 7 methyl) and 3 *cis* double bonds
- triply repeated stereotriad at $C_{2\text{-}4}$, $C_{12\text{-}10}$ and $C_{18\text{-}20}$

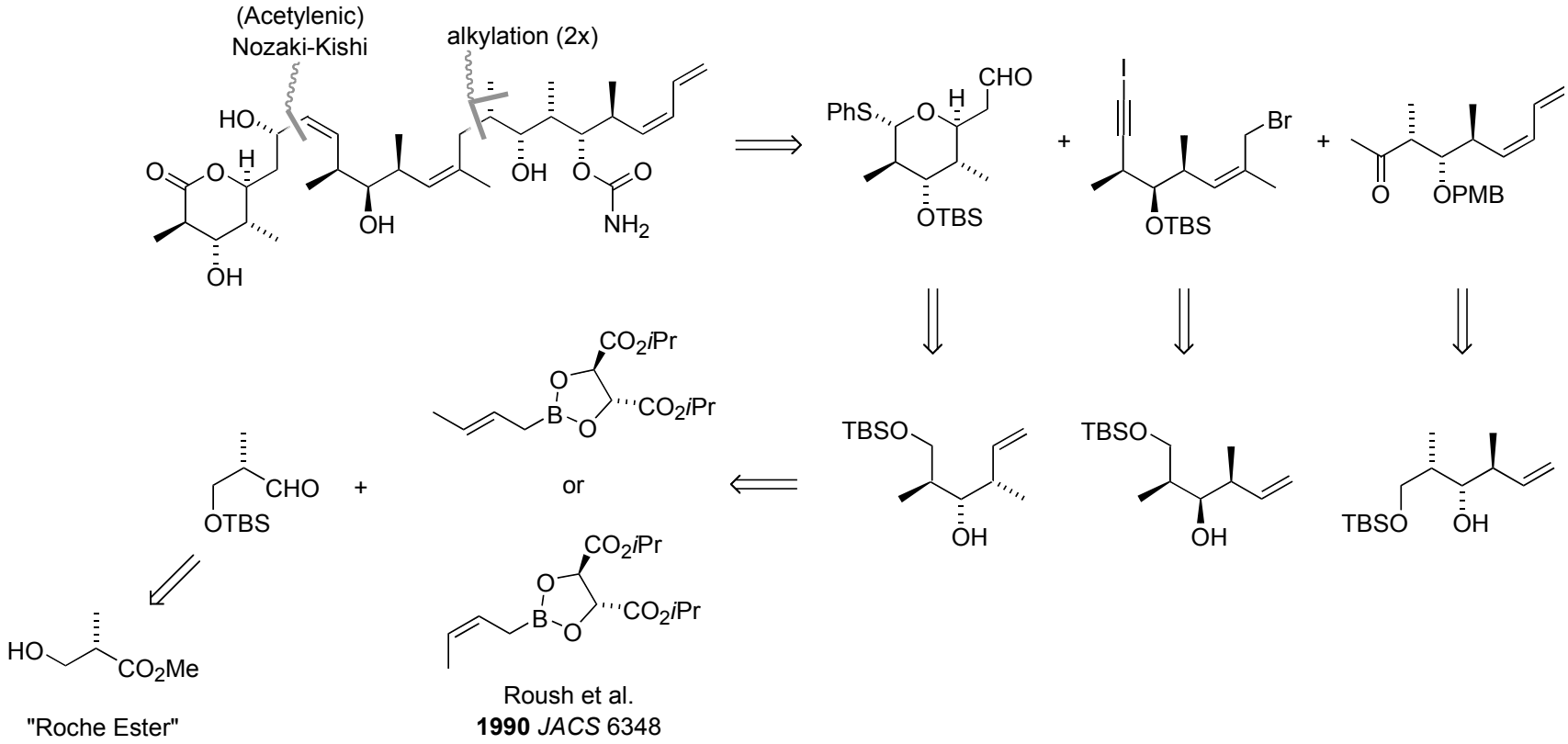
- Five academic research groups have reported total syntheses
- numerous (at least 26) fragment syntheses also published
- review: Paterson, I.; Florence, G. J. *Eur. J. Org. Chem.* **2003**, 2193

- isolated (9 mg) from extracts of the marine sponge *Discodermia dissoluta*
- "all discodermolide used for late preclinical research and development activities as well as for the ongoing clinical research trial has been supplied by total synthesis."

- the most potent known microtubule-stabilizing agent known
- undergoing phase I clinical trials (Novartis)
- potent inhibitor of tumor cell growth in vitro (including paclitaxel- and epothilone-resistant cells), and in mouse models

Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054

- 36 steps (24 steps longest linear sequence)
- 4.5% overall yield (9 mg prepared)

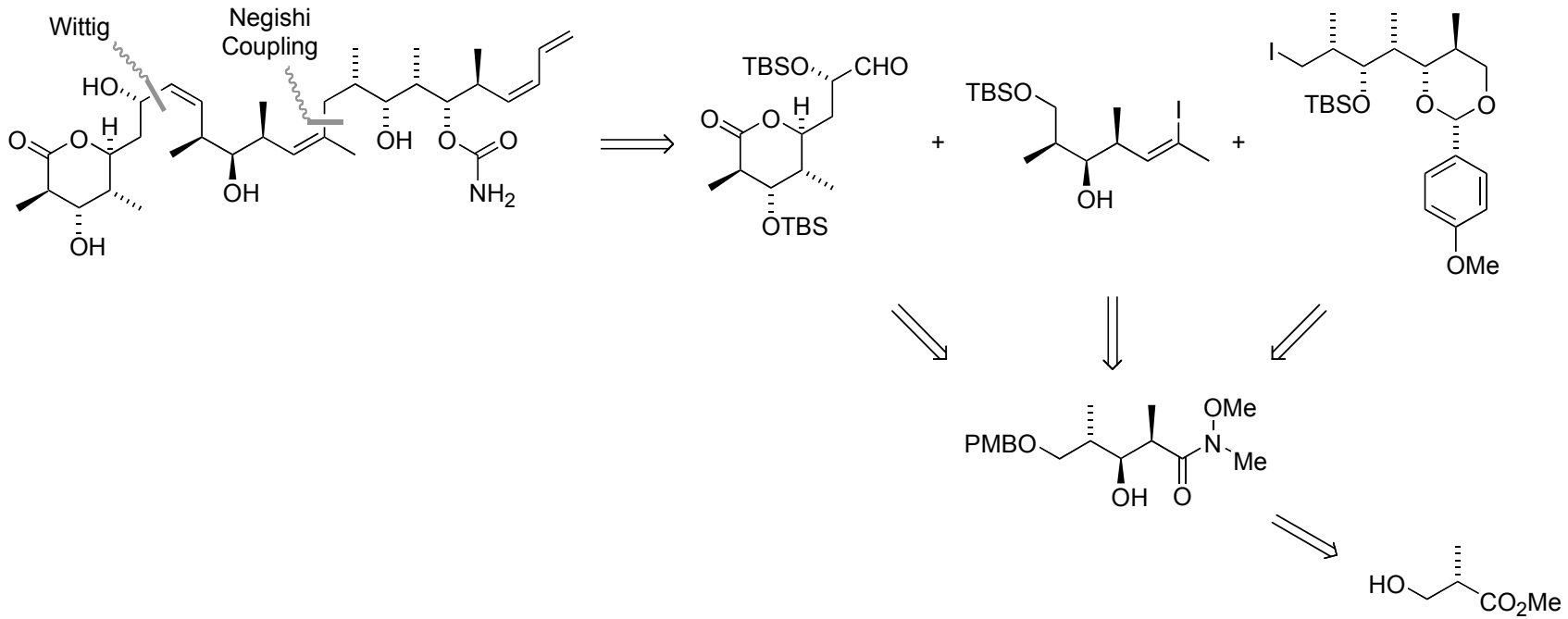


Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6098

- 27 steps
- <<1% overall yield (3 mg prepared)
- Disconections as above but Olefinic Nozaki-Kishi and mono-alkylation of ethyl ketone (not bis-alkylation of methyl ketone)

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

- 37 steps (24 steps longest linear sequence)
- 6% overall yield (1.04 g prepared)

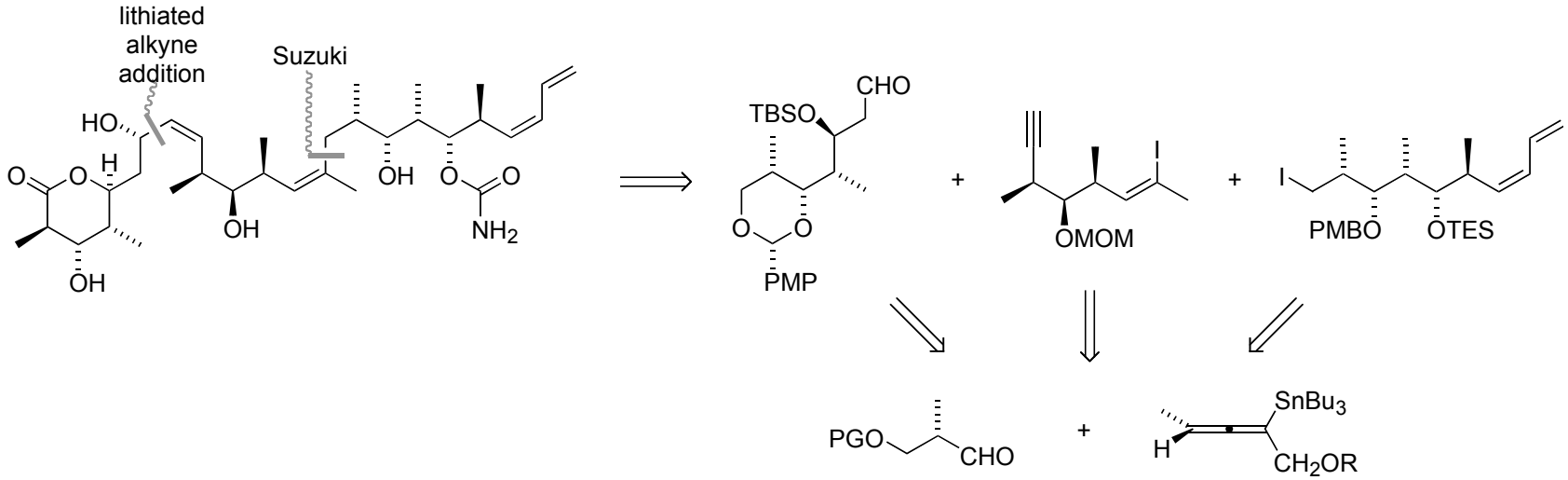


- Witting salt required 12.8 kBar (185 000 psi), 14 days to form; Witting rxn: 59-69% yld, 15-24:1 *Z*/*E*

- fix: Smith III, A. B.; Freeze, S.; Brouard, I.; Hirose, T. *Org. Lett.* **2003**, *5*, 4405
- MOM group in place of TBS - no pressure needed for Wittig salt formation but Wittig rxn: 51%, 4:1 *Z*/*E*

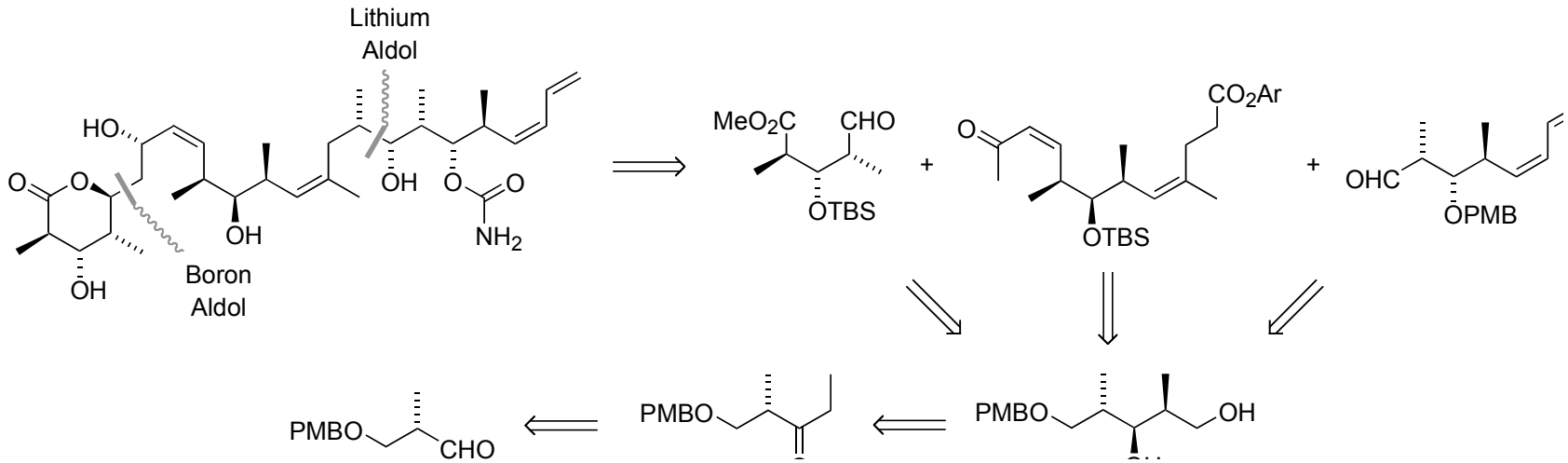
Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885

- 39 steps (29 steps longest linear sequence)
- 2.2% overall yield (8 mg prepared)

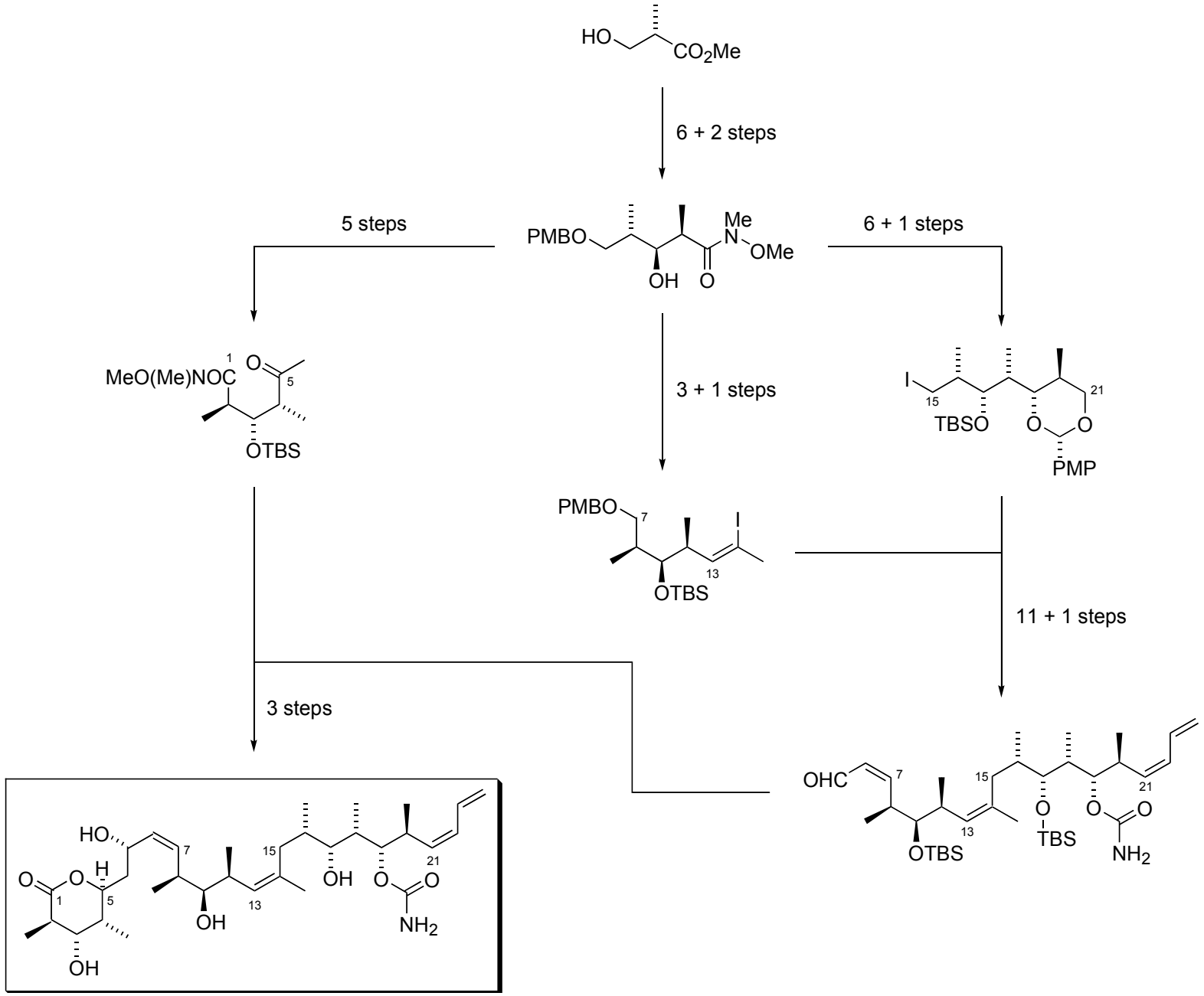


Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereinig, N. *Org. Lett.* **2003**, *5*, 35

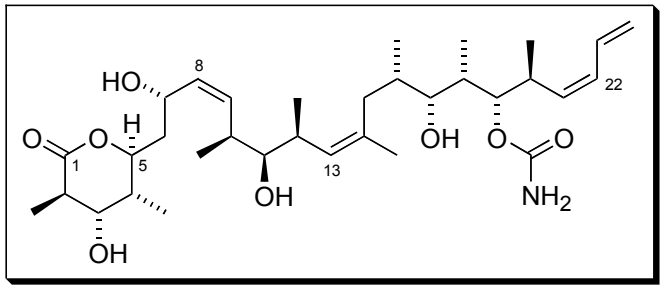
- 2nd generation approach
- 35 steps (24 steps longest linear sequence)
- 5.1% overall yield

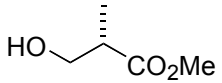


Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide

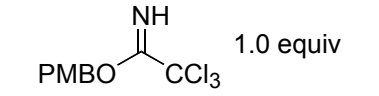


Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide

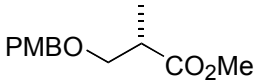




33 kg



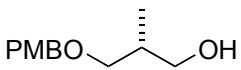
cat. PPTS,
CH_2Cl_2/cyclohexane
quant.



67 kg
[oil]

xs $LiBH_4$

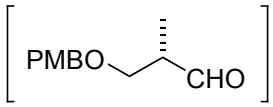
THF/EtOH
quant.



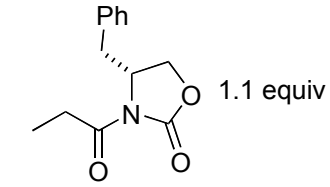
50 kg
[oil]

cat. TEMPO,
1.3 equiv NaOCl

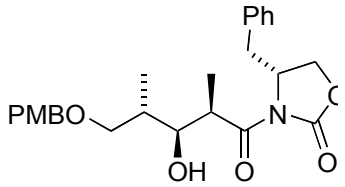
KBr, $KHCO_3$,
CH_2Cl_2, H_2O



29 kg
[unstable oil]



1.6 equiv *n*-Bu_2BOTf,
1.8 equiv Et_3N, CH_2Cl_2
46 - 55%

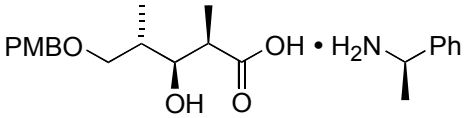


19 kg
[solid]

1. LiOH, H_2O_2, MeOH, H_2O;
   HCl, toluene

2. 1.05 equiv (*R*)-$PhCH(CH_3)NH_2$,
   toluene

84%

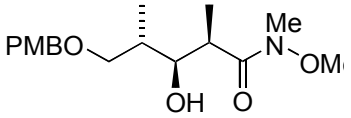


19 kg
[solid]

1. HCl, CH_2Cl_2/H_2O

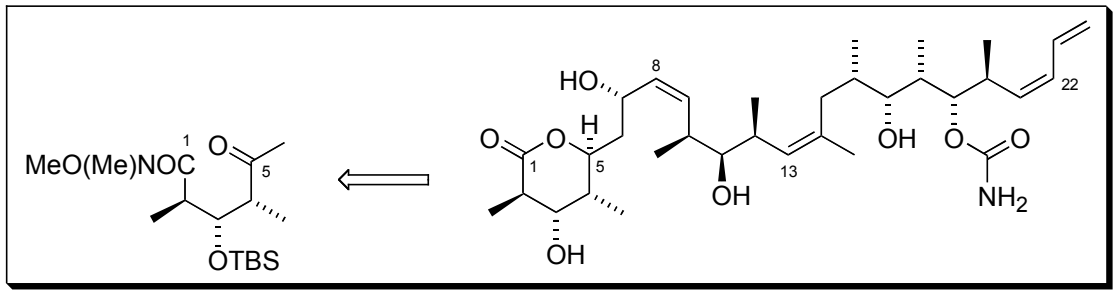
2. 1.05 equiv *N*-Me-piperidine,
   1.00 equiv *i*-BuOCOCl,
   CH_2Cl_2;
   1.25 equiv MeONHMe•HCl,
   1.30 equiv *N*-Me-piperidine

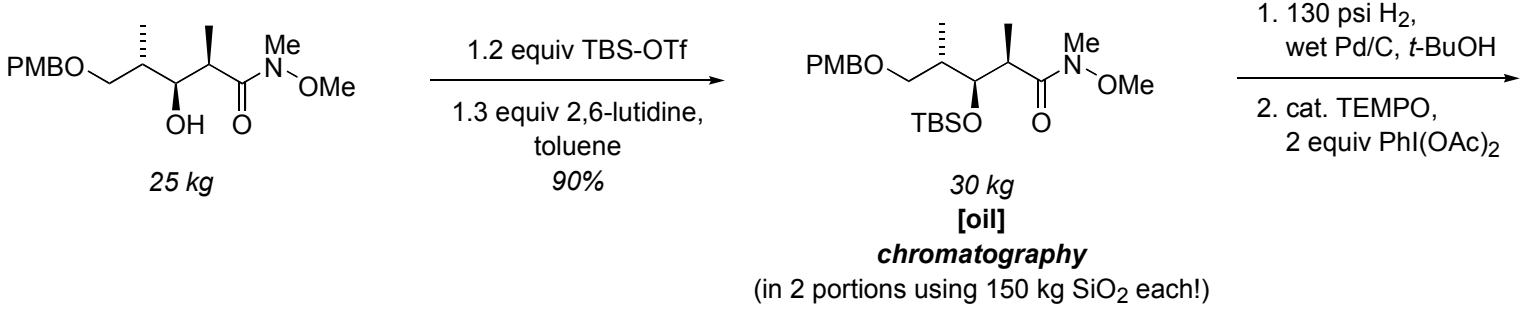
80%



29 kg
[oil]
77% purity

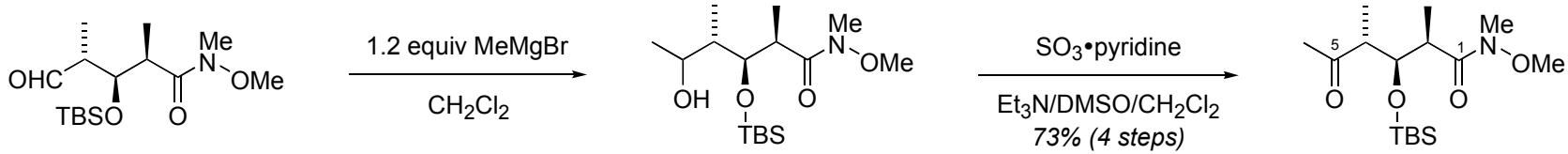
Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide





25 kg

30 kg
[oil]
chromatography
(in 2 portions using 150 kg SiO_2 each!)

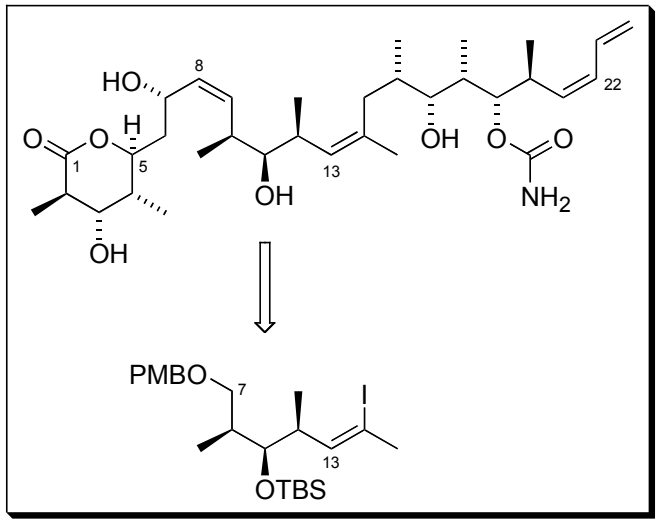


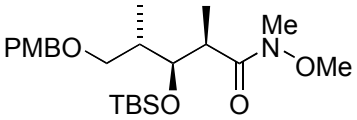
2.3 kg
[oil]

1.6 kg
[oil]

0.94 kg
[oil]
chromatography

Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide



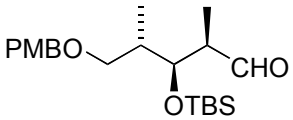


14 kg

1.5 equiv Red-Al

toluene

68%

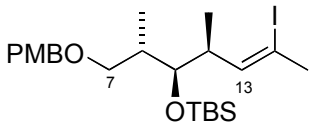


8.3 kg
[oil]
chromatography

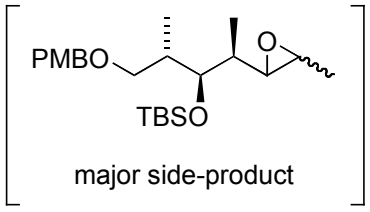
1.4 equiv NaHMDS,
1.6 equiv $Ph_3PCH(I)CH_3$

THF

31% (15:1 Z/E)

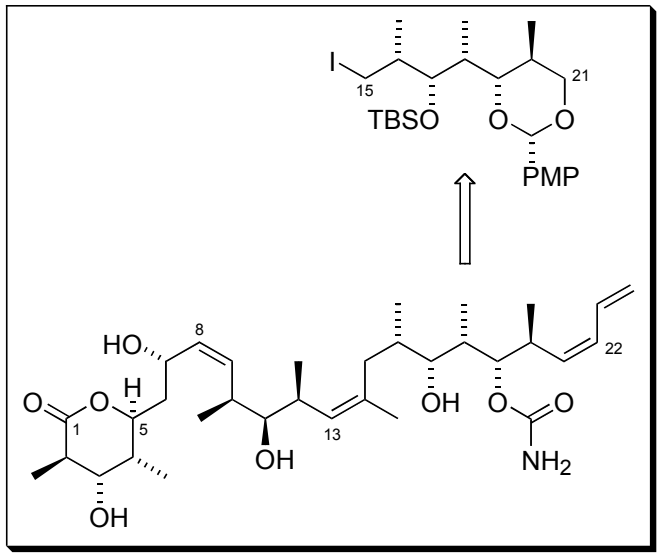


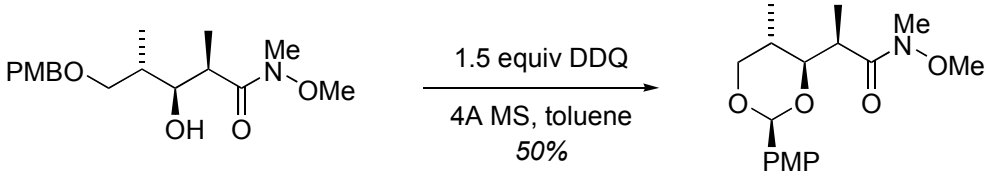
1.08 kg
[oil]
chromatography



major side-product

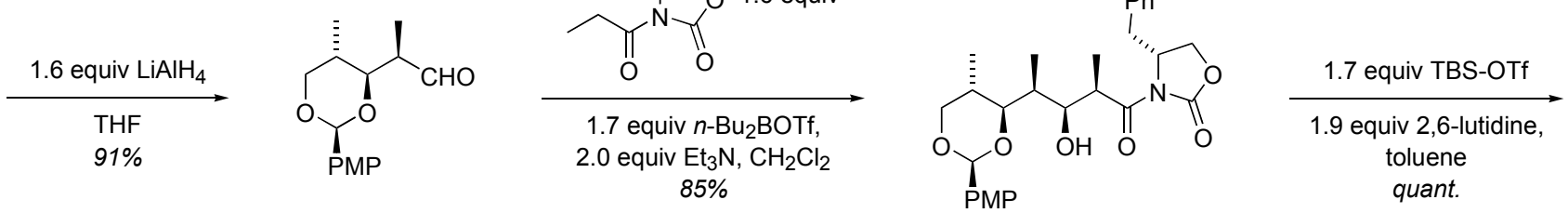
Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide





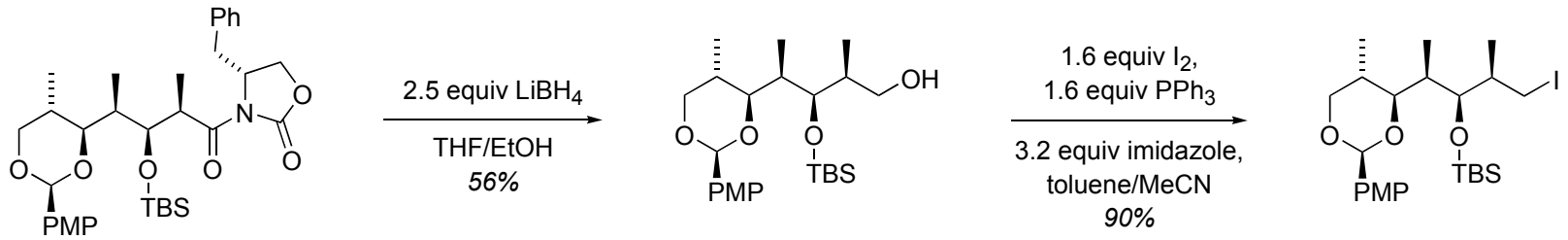
18 kg

6.9 kg
[solid]



1.5 kg
[solid]

2.1 kg
[unstable solid]

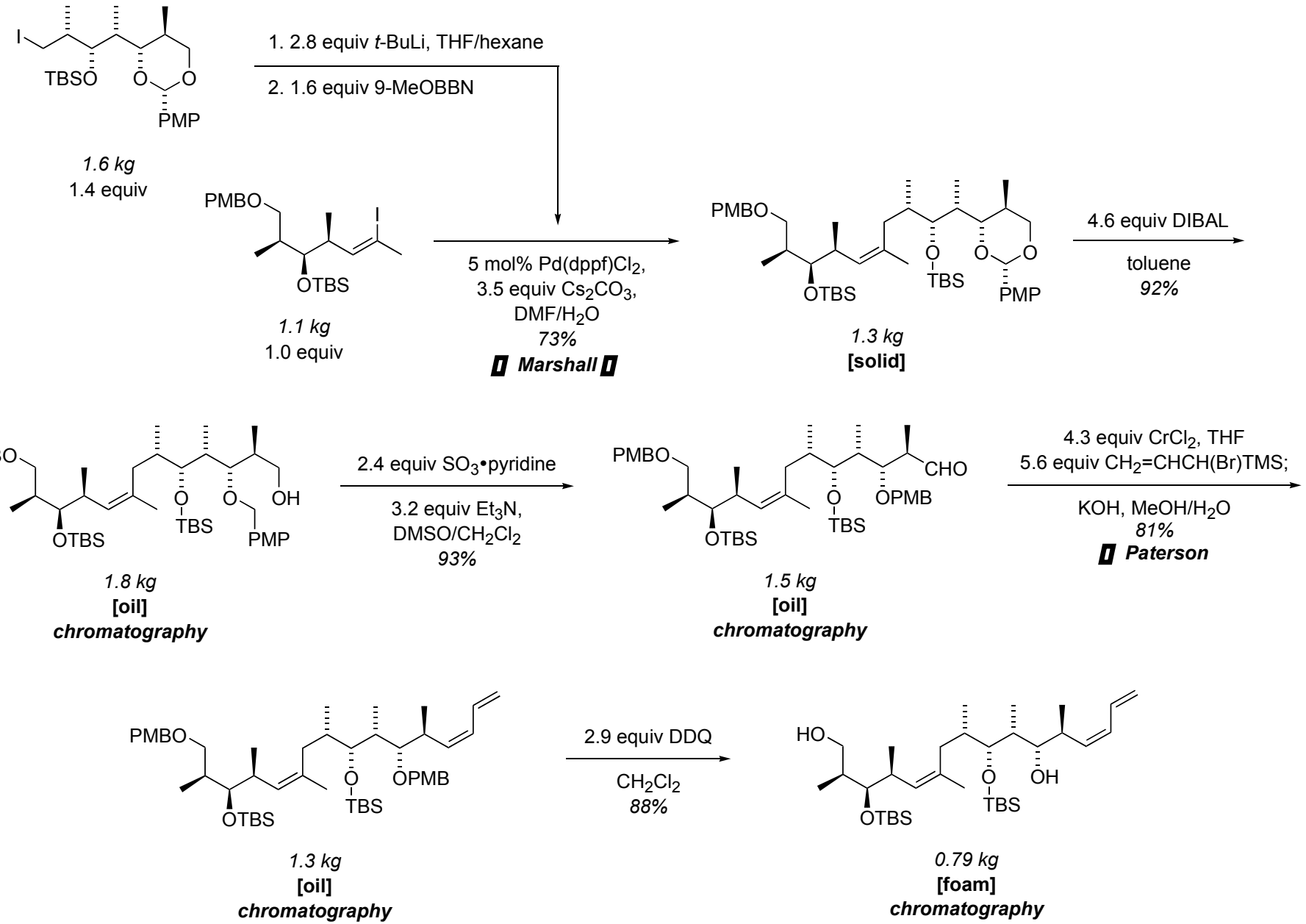


2.9 kg
[oil]

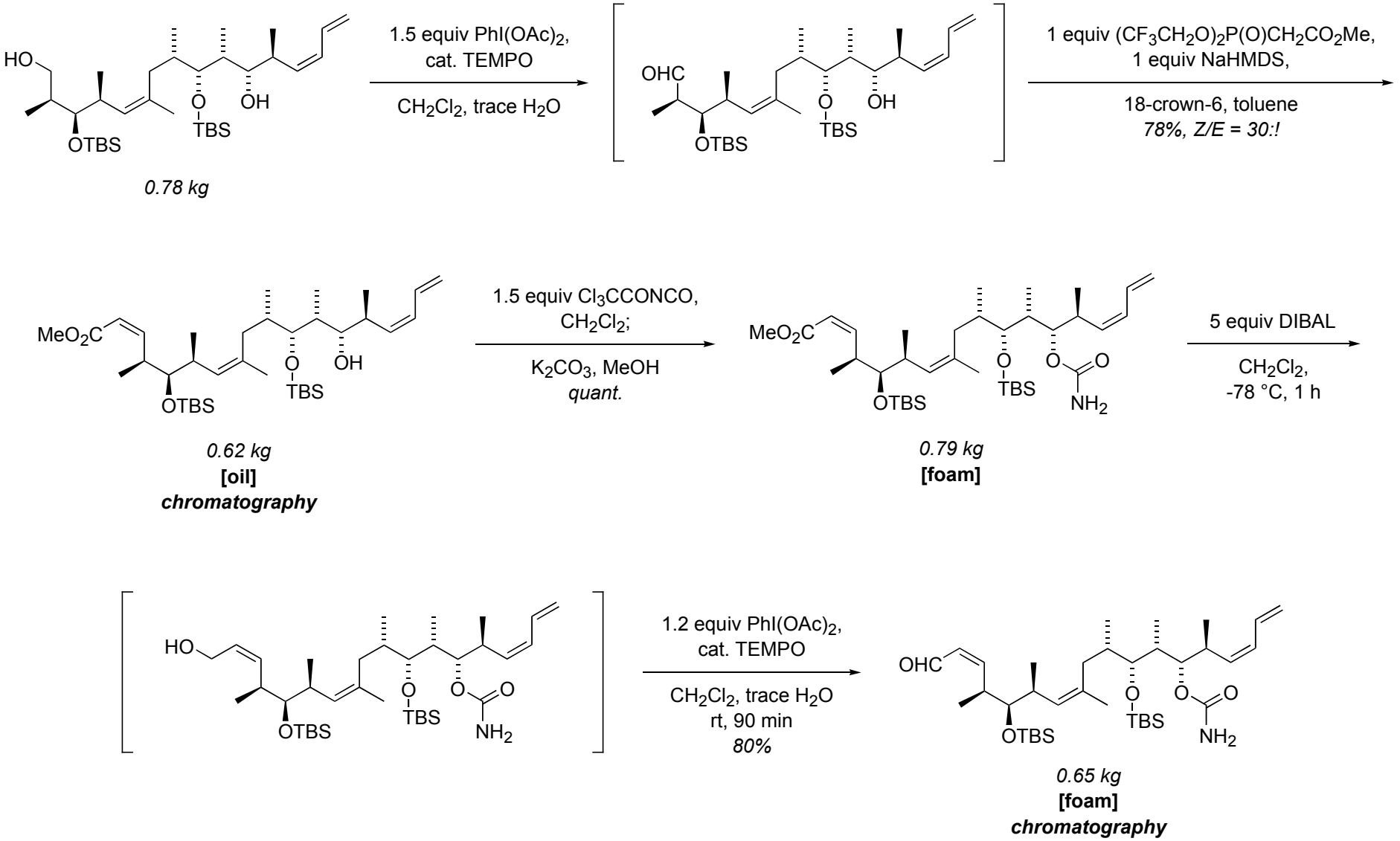
2.0 kg
[oil]
chromatography

3.1 kg
[light-sensitive oil]
chromatography

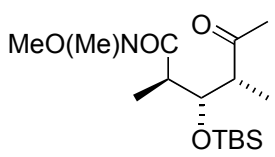
Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide



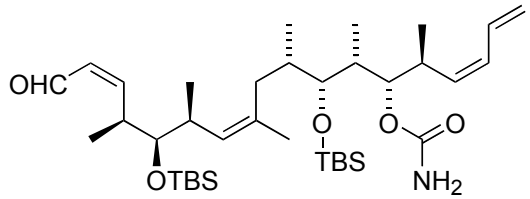
Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide



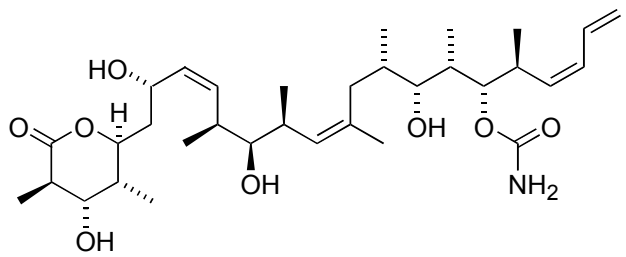
Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide



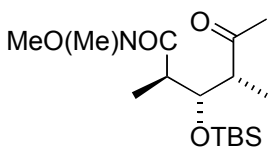
0.94 kg (2.8 mol)
$C_8H_{12}O_3$(TBS)(N(Me)OMe)
Mol. Wt.: 331.5



647 g (0.97 mol)
$C_{25}H_{39}NO_5(TBS)_2$
Mol. Wt.: 664.1



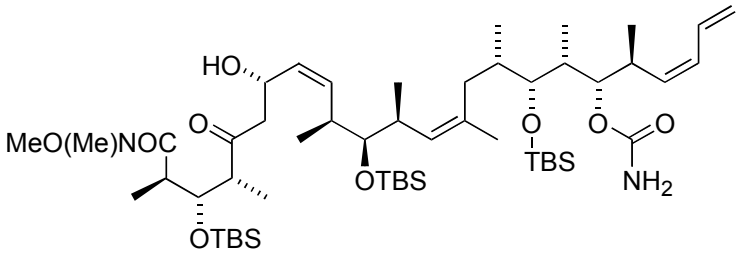
(+)-discodermolide
$C_{33}H_{55}NO_8$
Mol. Wt.: 593.8



234 g
6.6 equiv

1. 5.4 equiv (+)-DIP-Cl,
6.6 equiv Et_3N, Et_2O

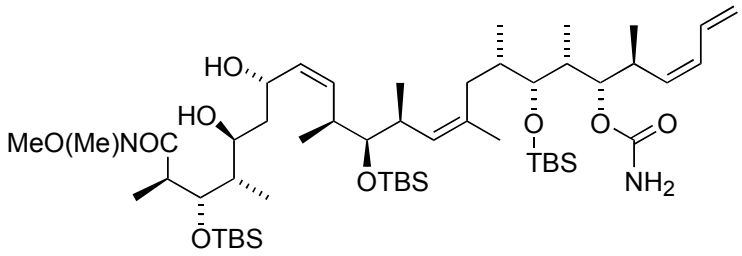
2. 1.0 equiv (*71 g)* Aldehyde
63% (dr ~ 4:1)



67 g
[foam]
chromatography

xs $[Me_4N]B(OAc)_3H$

AcOH/THF
73%



76 g
[foam]
chromatography

3 N HCl, MeOH

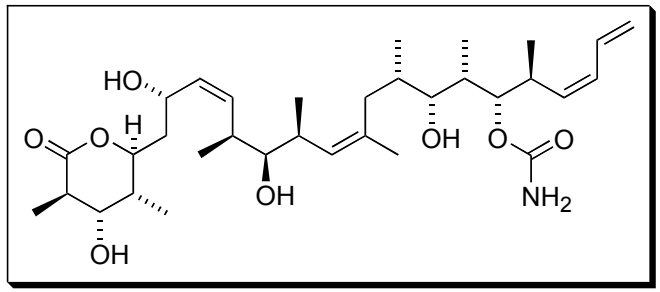
61%

(+)-discodermolide

28 g
[foam]
chromatography

recrystallize
65 g from $MeCN/H_2O$
 61.7 g (monohydrate)

Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide



• 60 g, 39 steps, 17 chromatographic purifications, 20 months, 43 chemists

• "The end game is far from ideal ... The arduous chromatography of the final aldol coupling product is clearly not practical to move into production ..."

• "The success of this project ... sends a positive message to ... the synthetic academic community ... that: 'your work need not just be of academic interest' and it may be worth taking a few risks."

• "The option of optimizing the present synthesis further or replacing it with a better one is a topic of our ongoing studies ..."

• "We anticipate that our new third-generation approach will further simplify the synthesis and reduce the cost of the clinical material." *A. B. Smith III*

• Smith III 2nd generation approach: 34 steps (24 longest linear sequence), 6% overall yield
• Novartis-Smith-Paterson approach: 39 steps (26 longest linear sequence), 0.65% overall yield