Large-Scale Synthesis of (+)-Discodermolide

-- The Hybridized Novartis-Smith-Paterson Approach

Stuart J. Michel, et al. *Org. Process Res. Dev.* **2004**, *8*, 92, 101, 107, 113 and 122.

Other References:

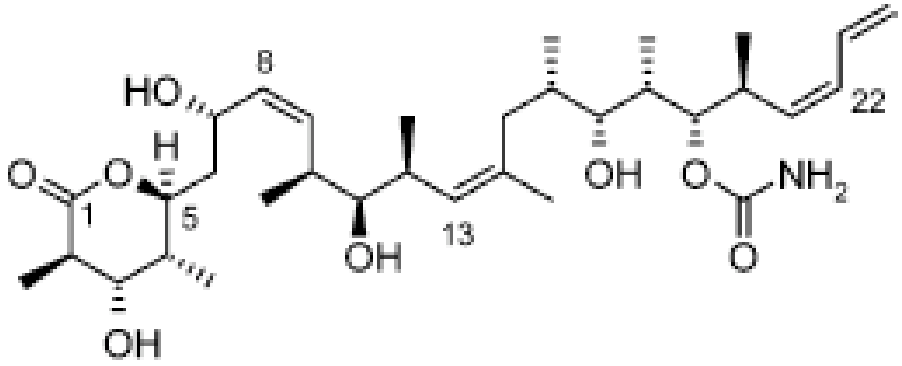
Amos B. Smith III, et al. *J. Am. Chem. Soc.* **2000**, *122,* 8654.

Ian Paterson, et al. *Angew. Chem., Int. Ed*. **2000**, *39*, 377.

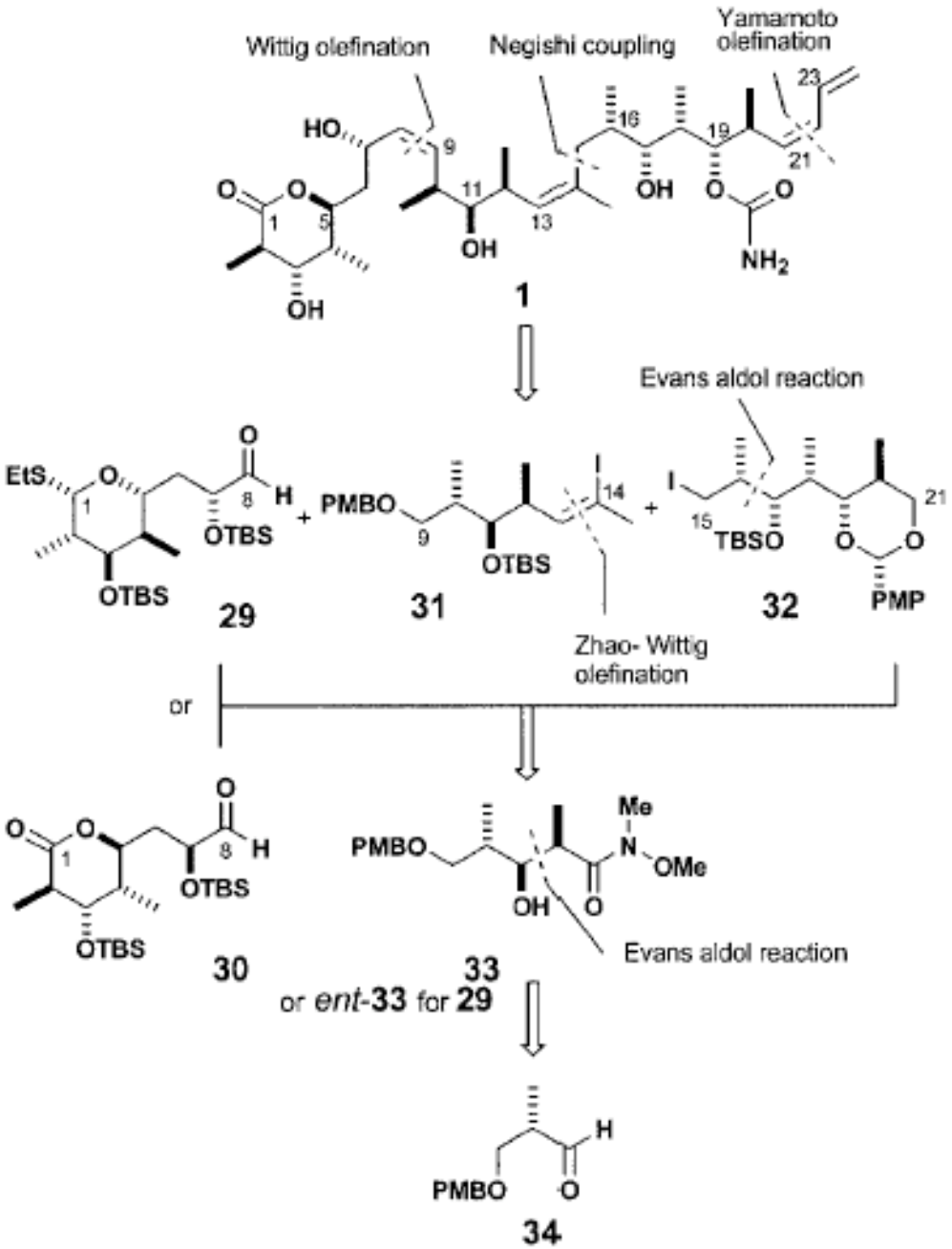
Yiqian Lian

3-11-04

Introduction to (+)-Discodermolide

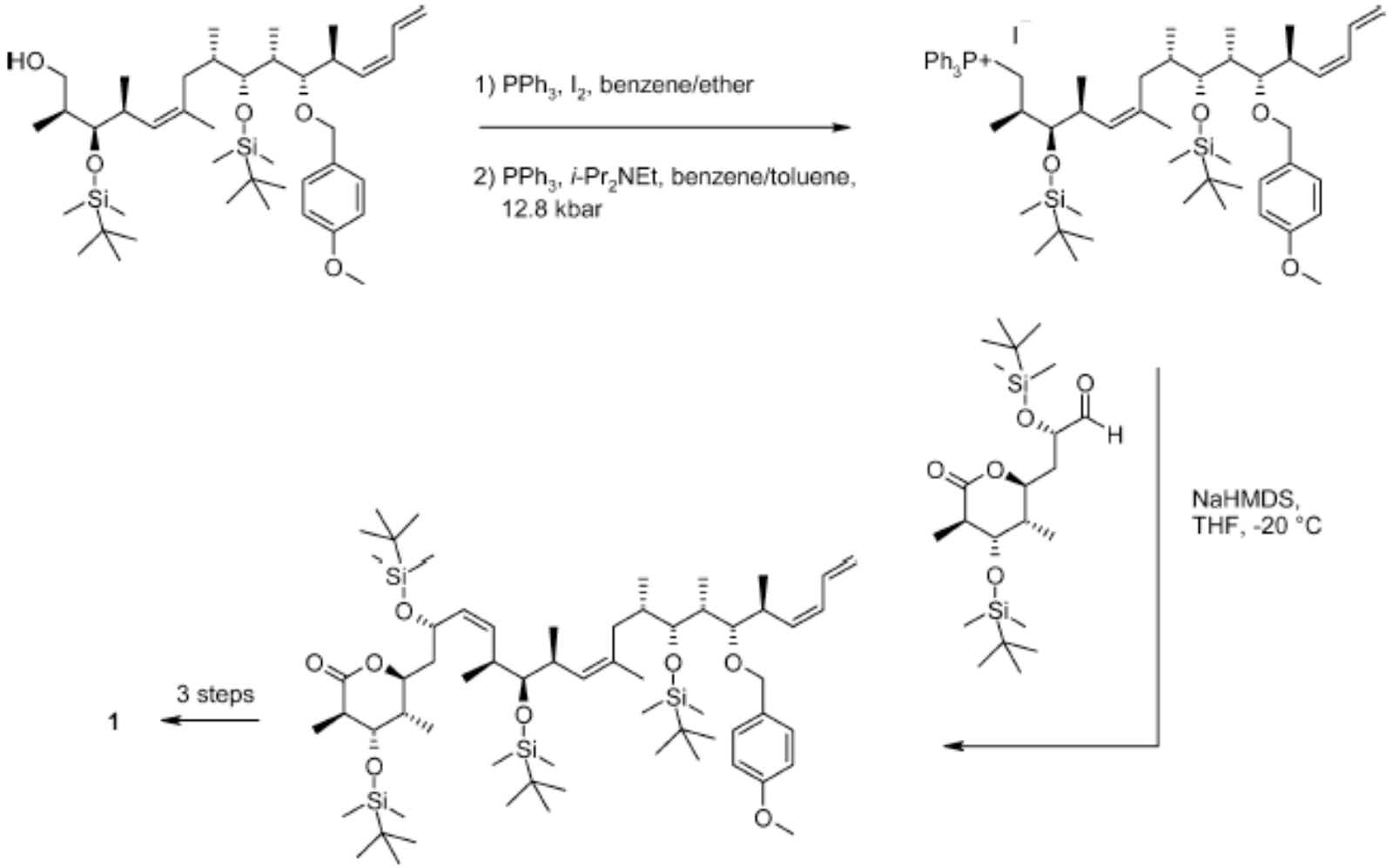


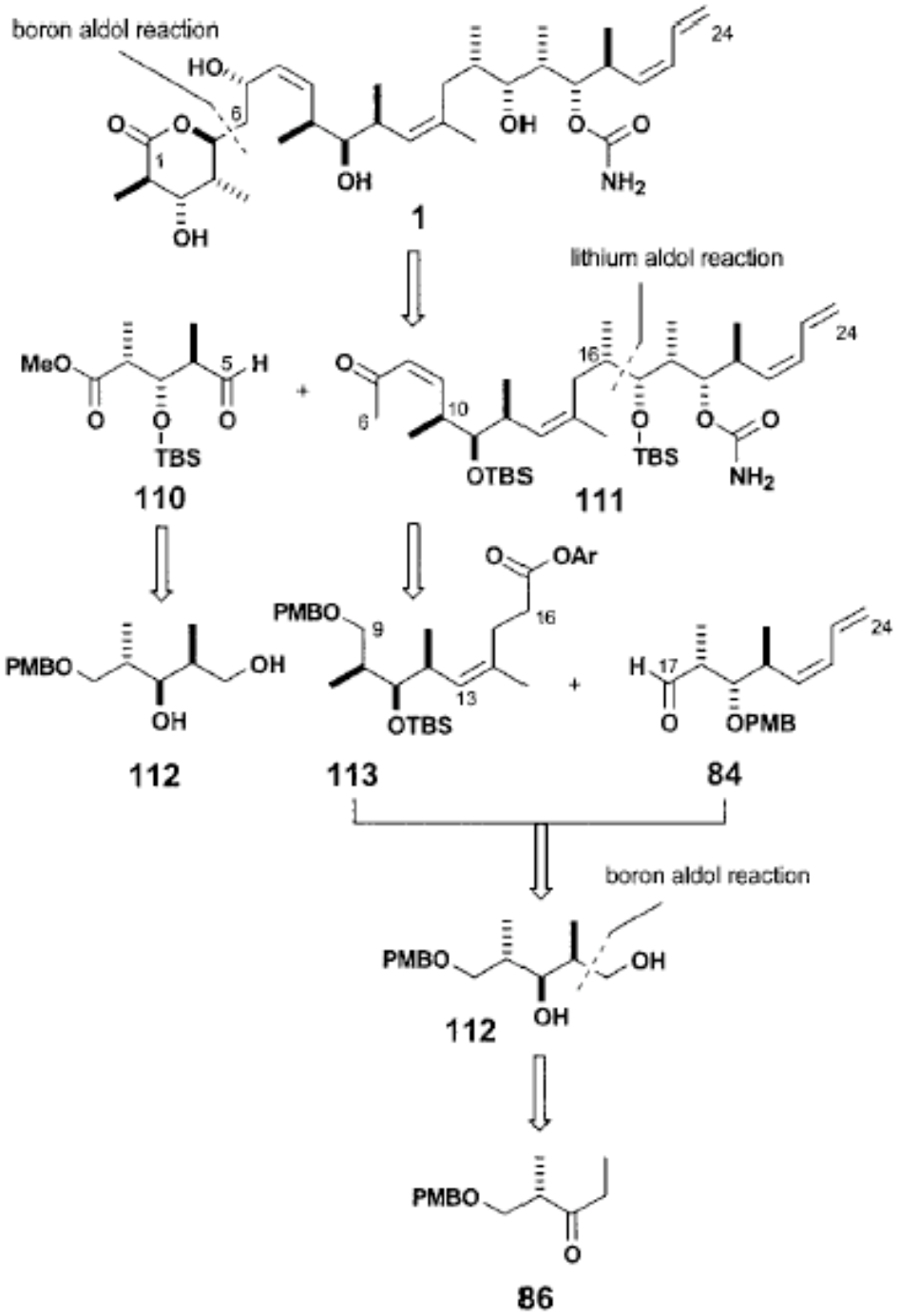
- A novel polyketide natural product first isolated from extracts of marine sponge *Discodermia dissoluta* by Harbor Branch Oceanographic Institution (JOC, 1990, 4912).
- One of a small, but structurally diverse collection of non-taxane microtubule-stabilizing (MTS) agents such as: the epothilones (EPO), eleutherobin and laulimalide.
- Discodermolide stabilizes microtubules faster, more potently than any of the other known MTS agents, is a potent inhibitor of tumor cell growth in vitro, including Taxol- and EPO-resistant cells.
- Currently undergoing phase I clinical trials.
- A linear polypropionate chain containing 13 stereocenters, (6 hydroxy-bearing, 7 methyl-bearing).
- Total syntheses: Schreiber (JACS, 1993 and 1996), Smith, Paterson, Marshall, Myles and Halstead.
- The compound supply for development cannot be met through isolation and purification, and attempts by fermentation has not been successful to date. All discodermolide used for late preclinical R&D activities and phase-I trial has been supplied by total synthesis.



Smith's Strategy

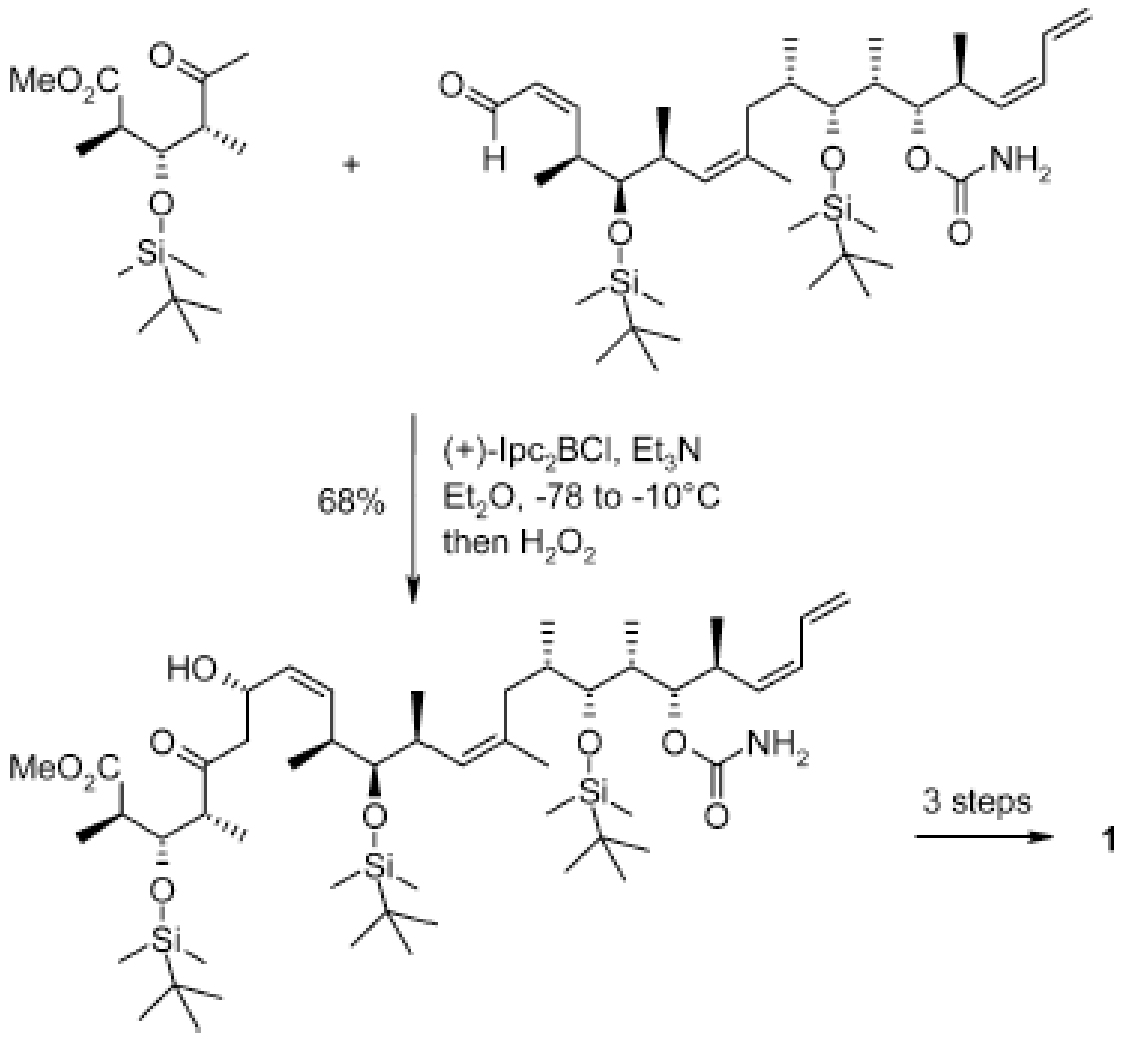
High-Pressure Phosphonium Salt Formation of Smith's Route



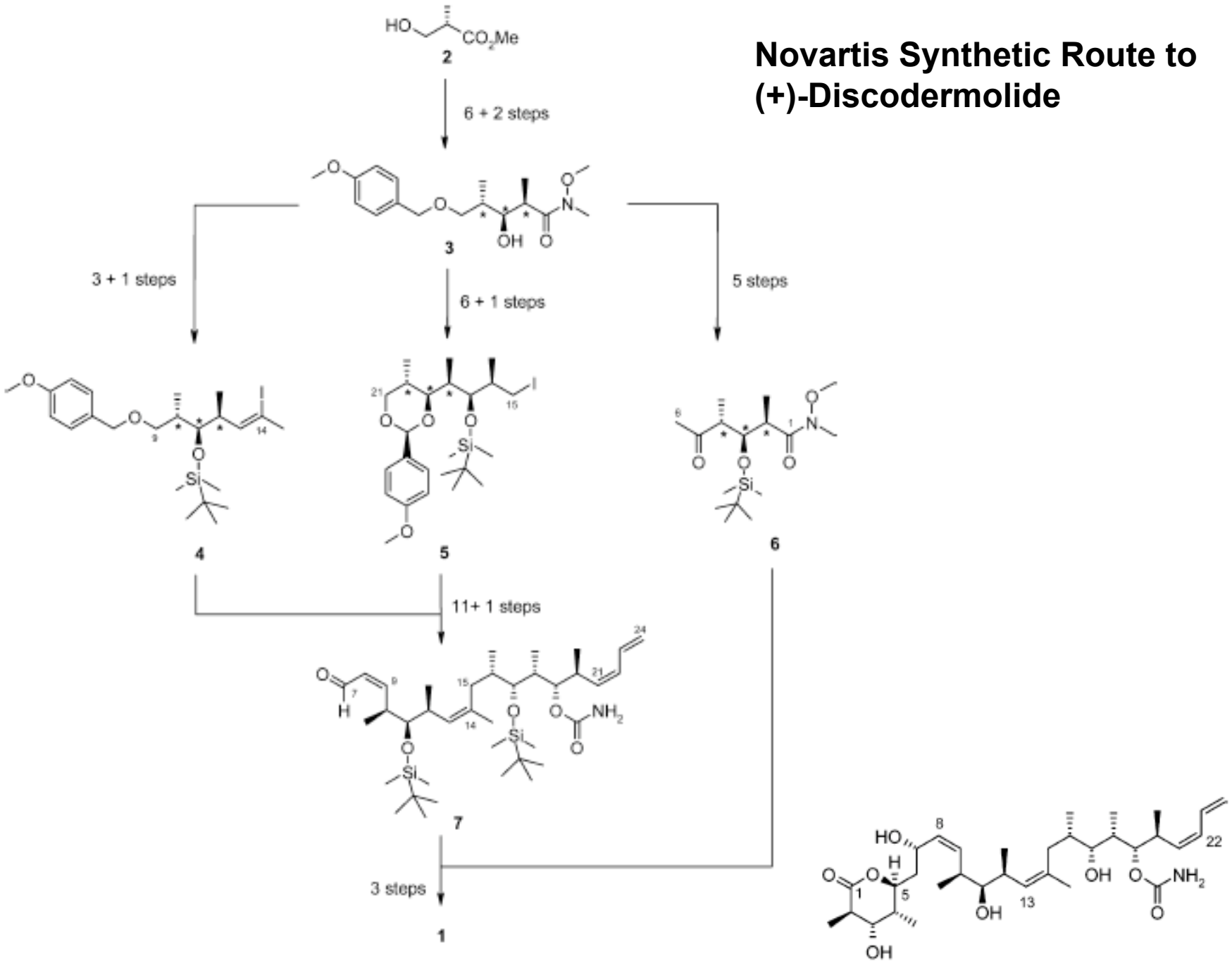


Paterson's Strategy

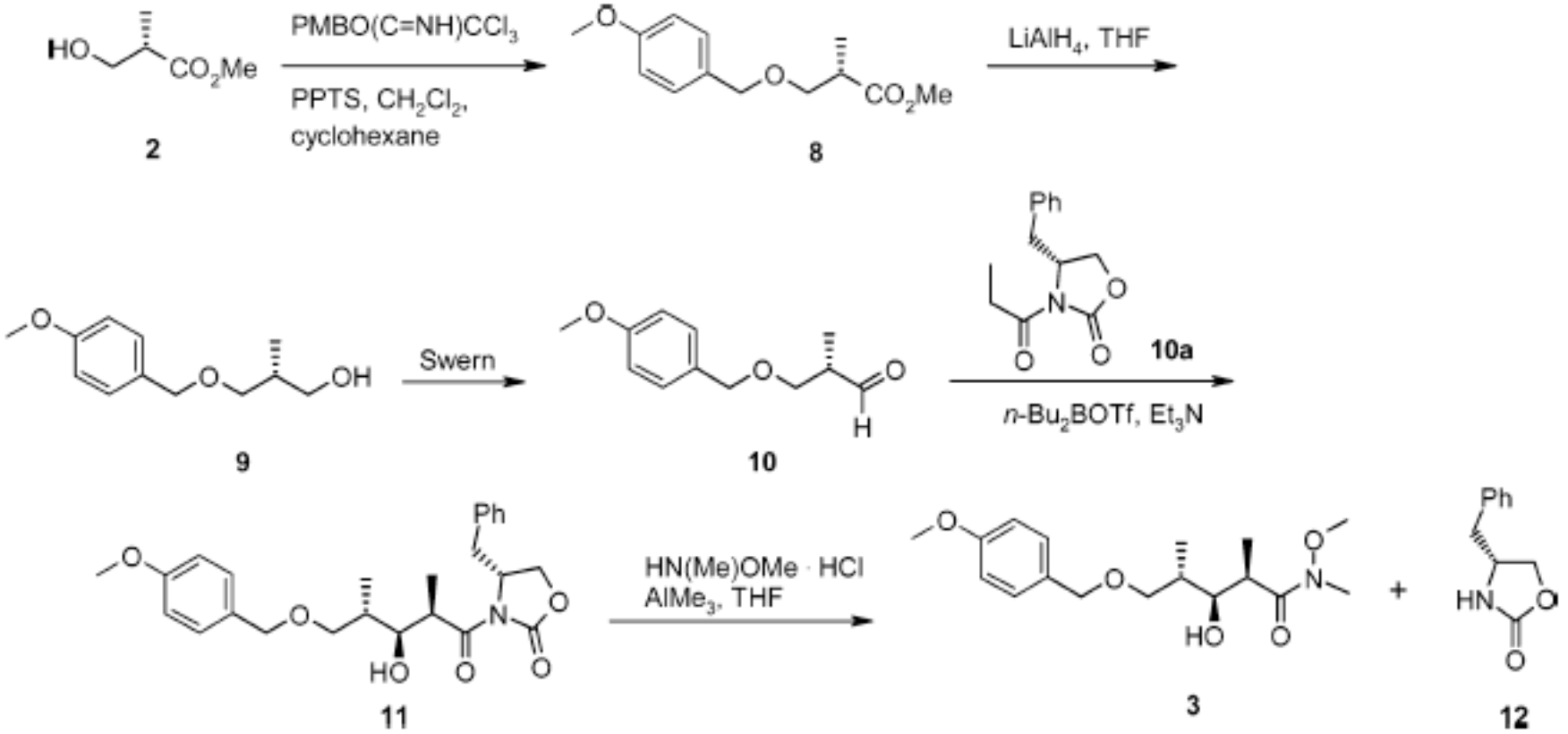
Last Steps of Paterson's Route



Novartis Synthetic Route to (+)-Discodermolide



Synthesis of the Common Precursor 3



2→8: 67.16 kg, > 98% yield.

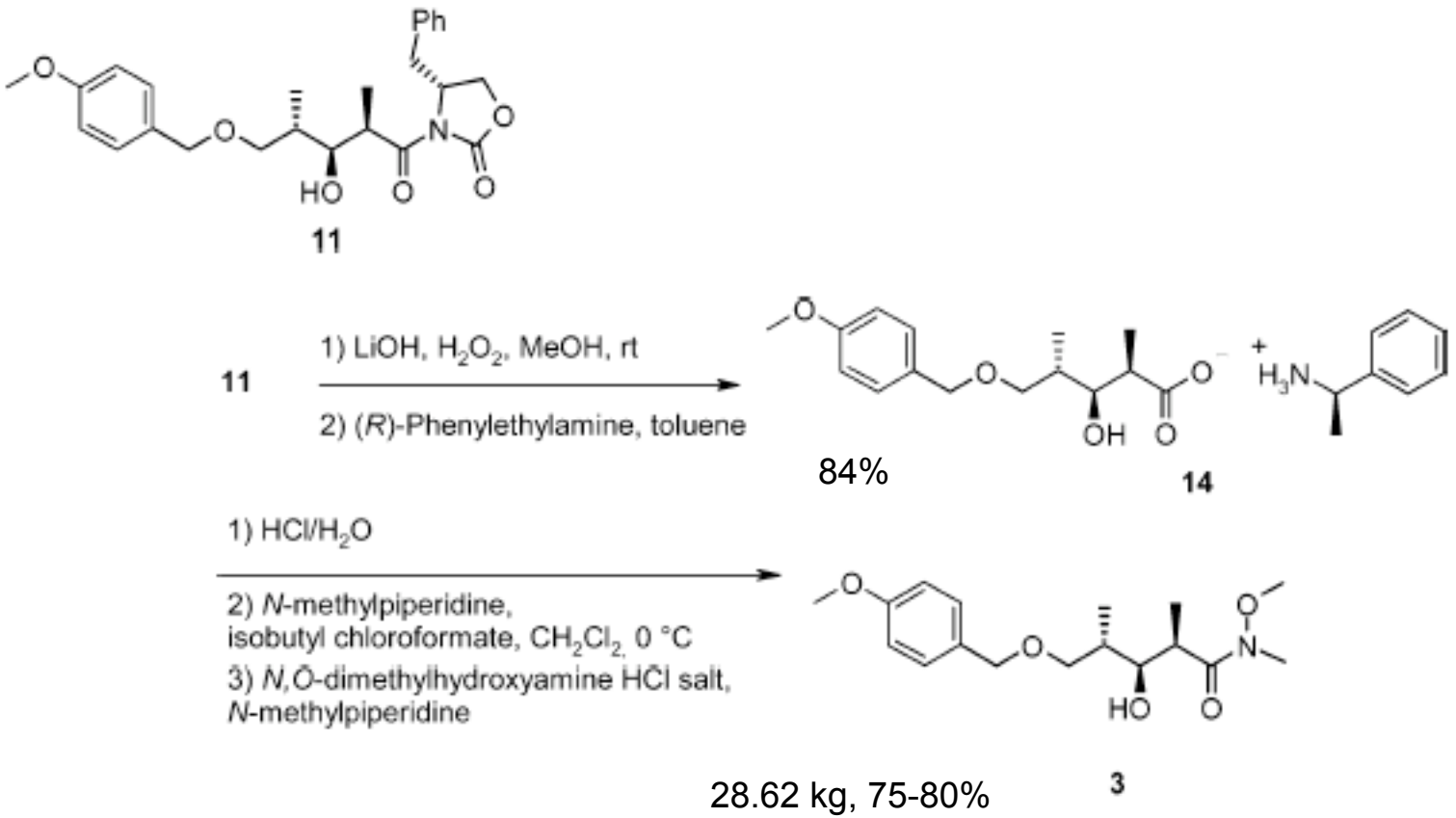
8→9: Filtration problematic; used $LiBH_4$ instead. > 98% yield.

9→10: Me_2S not environmentally friendly; TEMPO/bleach oxidation in DCM. quantitive yield.

10→11: 46-55% on 20-25 kg scale, (>75% on 20-50 g scale); quality of boron reagent important. aldol product **11** confirmed by X-ray analysis.

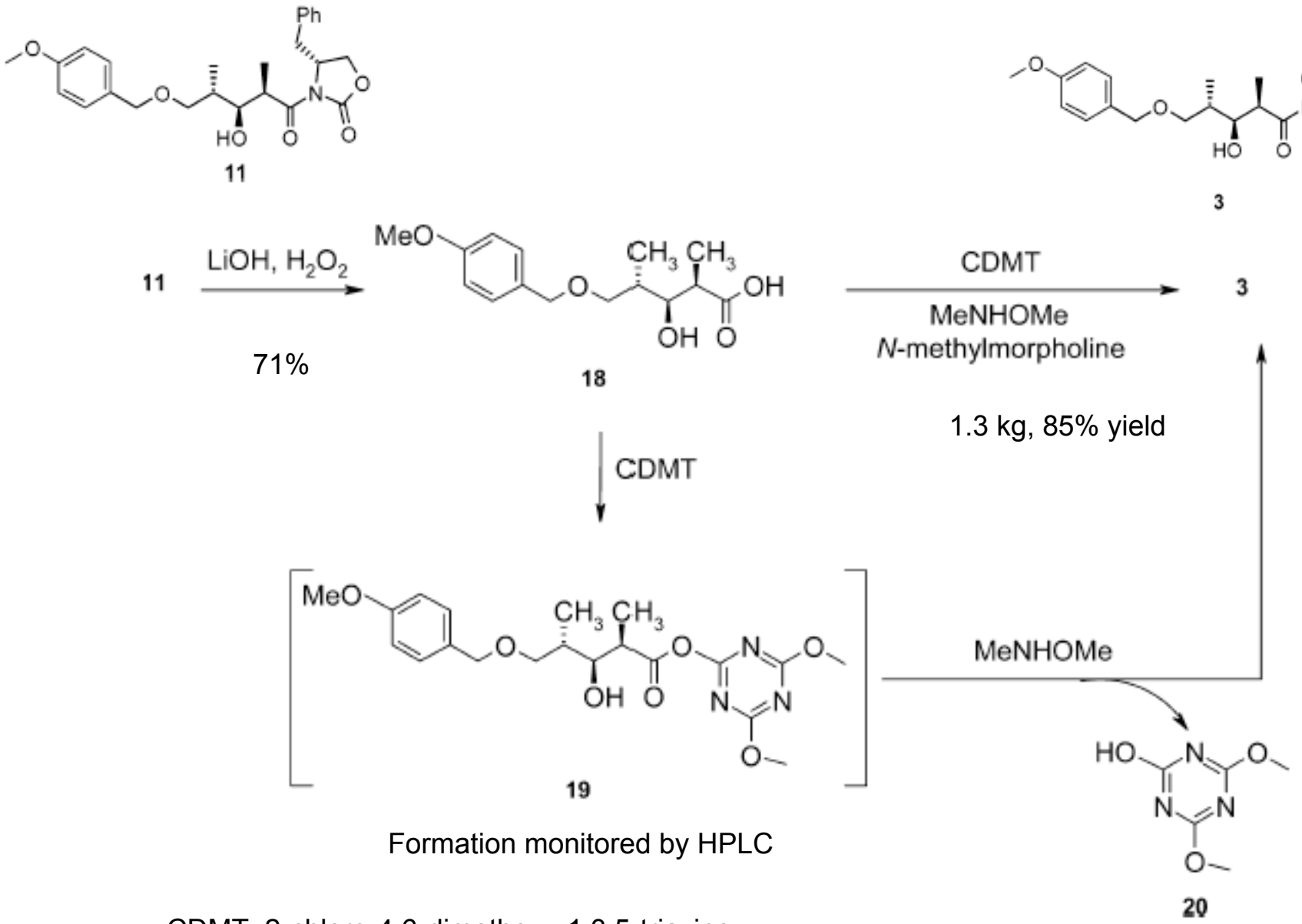
11→3: $AlMe_3$ pyrophoric; tried Al^iBu_3, 17.6 g, 75-80% yield, 85% purity. Competitive ring-opening reaction. Highly exothermic, unfeasible for scale-up.

Amide Formation Employing Chloroformate



- Crystallization of **14** at this stage is the first purification carried out thus far.

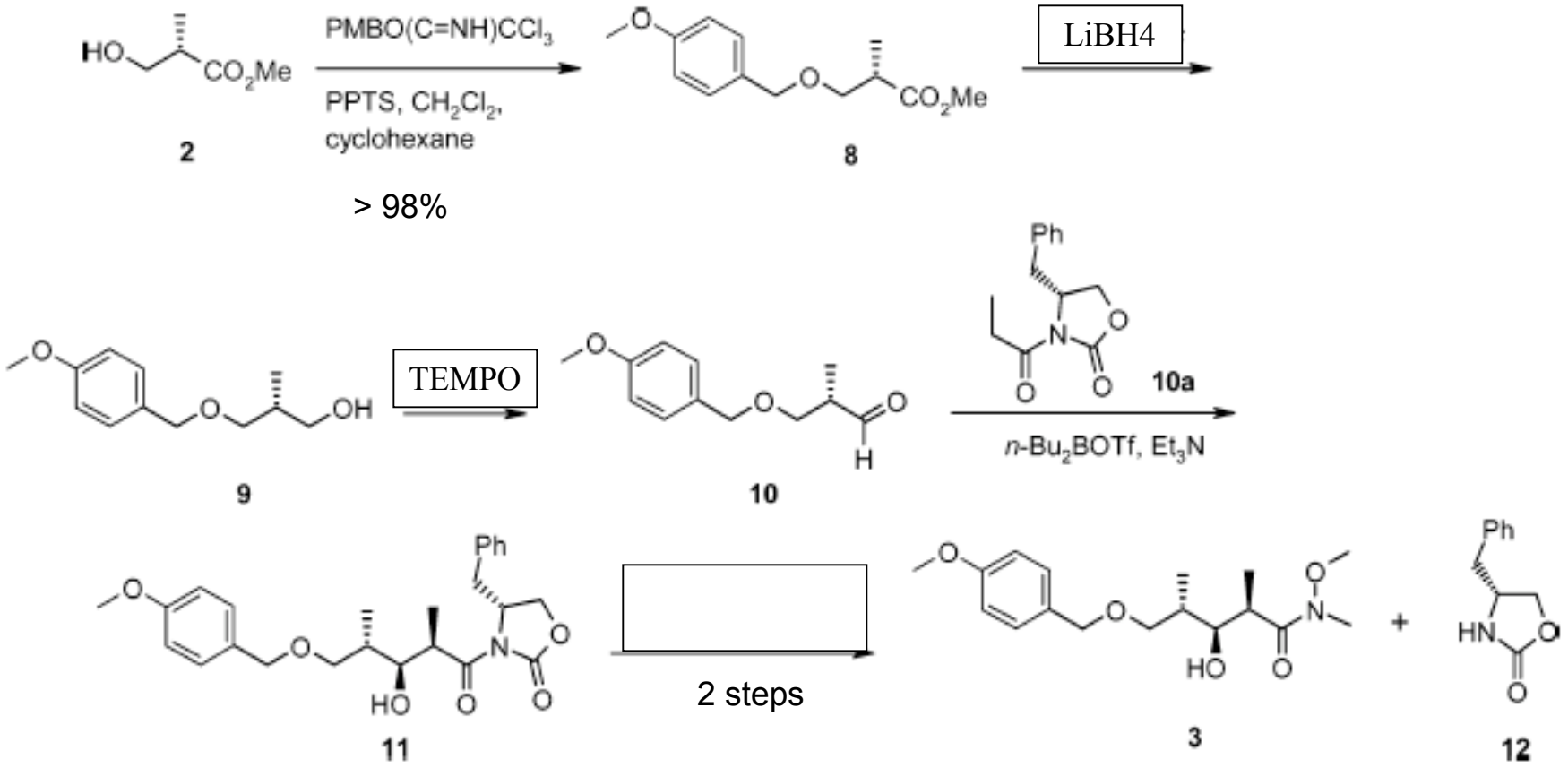
Amide Formation Employing CDMT



Formation monitored by HPLC

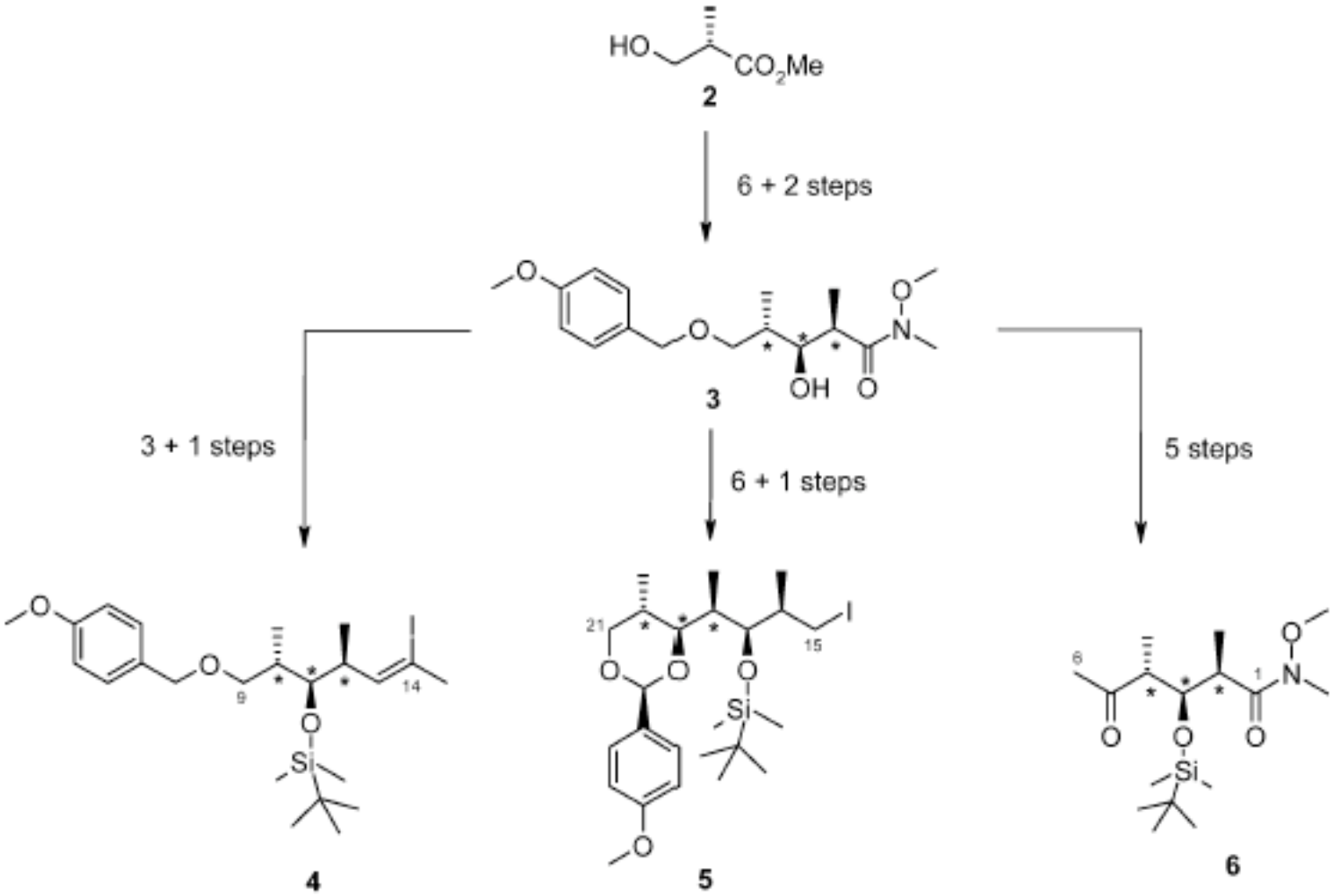
CDMT: 2-chloro-4,6-dimethoxy-1,3,5-triazine

Synthesis of the Common Precursor 3

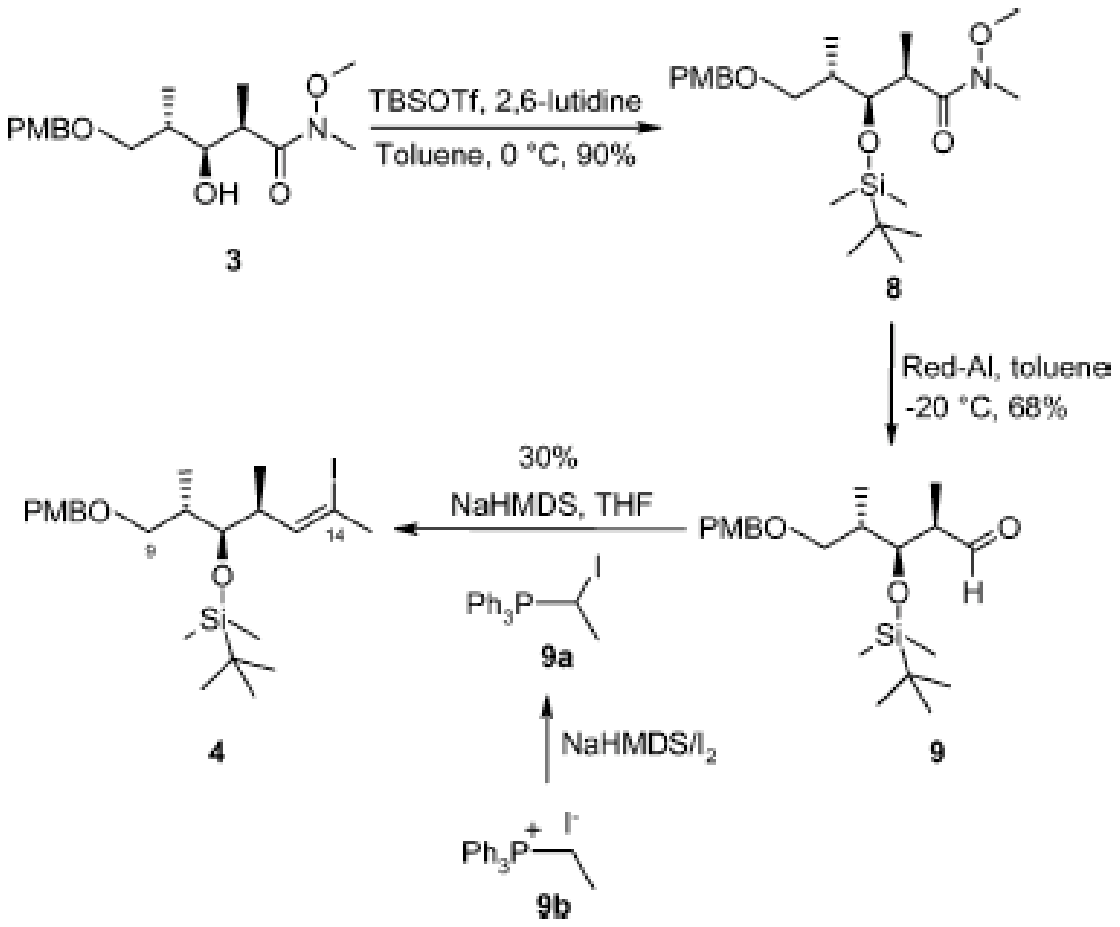


- Smith's procedure was modified to facilitate large-scale production in the pilot plant;
- Kilogram quantities of Weinreb amide **3** was prepared;
- Intermediate **3** was synthesized in six steps without chromatography.

Synthesis of Fragments C1-6 and C9-14



Synthesis of Fragment C9-14

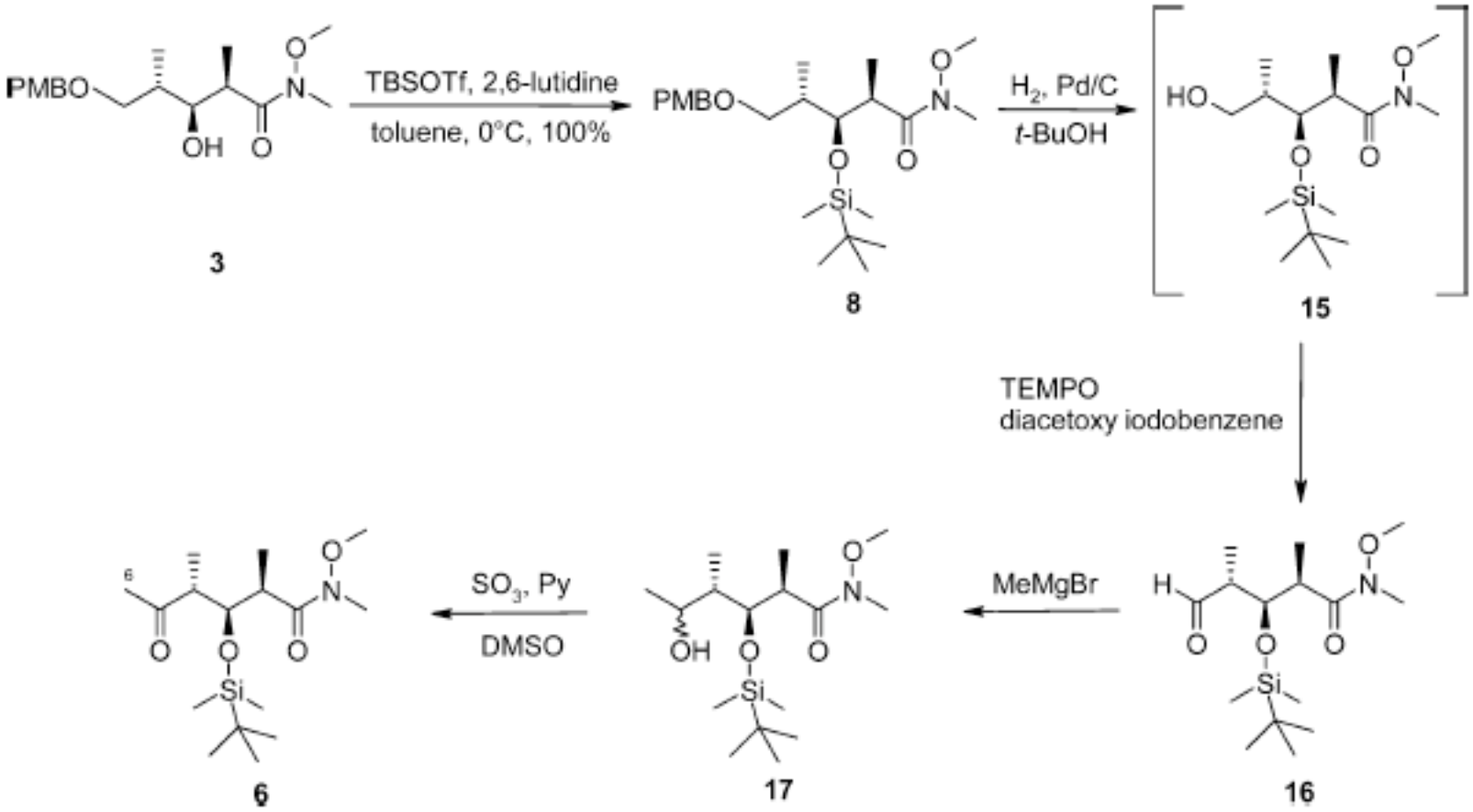


3→8: 30.4 kg, 90% yield, by chromatography (two portions);

8→9: Original procedure used DIBAL at -78 °C, and alcohol produced; Using Red-Al, Quality of **8**, reaction time and temperature crucial, Desilylation by-product, **9** stable at <-10 °C.

9→4: cis/trans: 15:1. One of the most difficult reactions for scale-up, max. scale of 2.5 kg of **9**. N-iodosuccinimide can be used to replace iodine.

Synthesis of Fragment C1-6



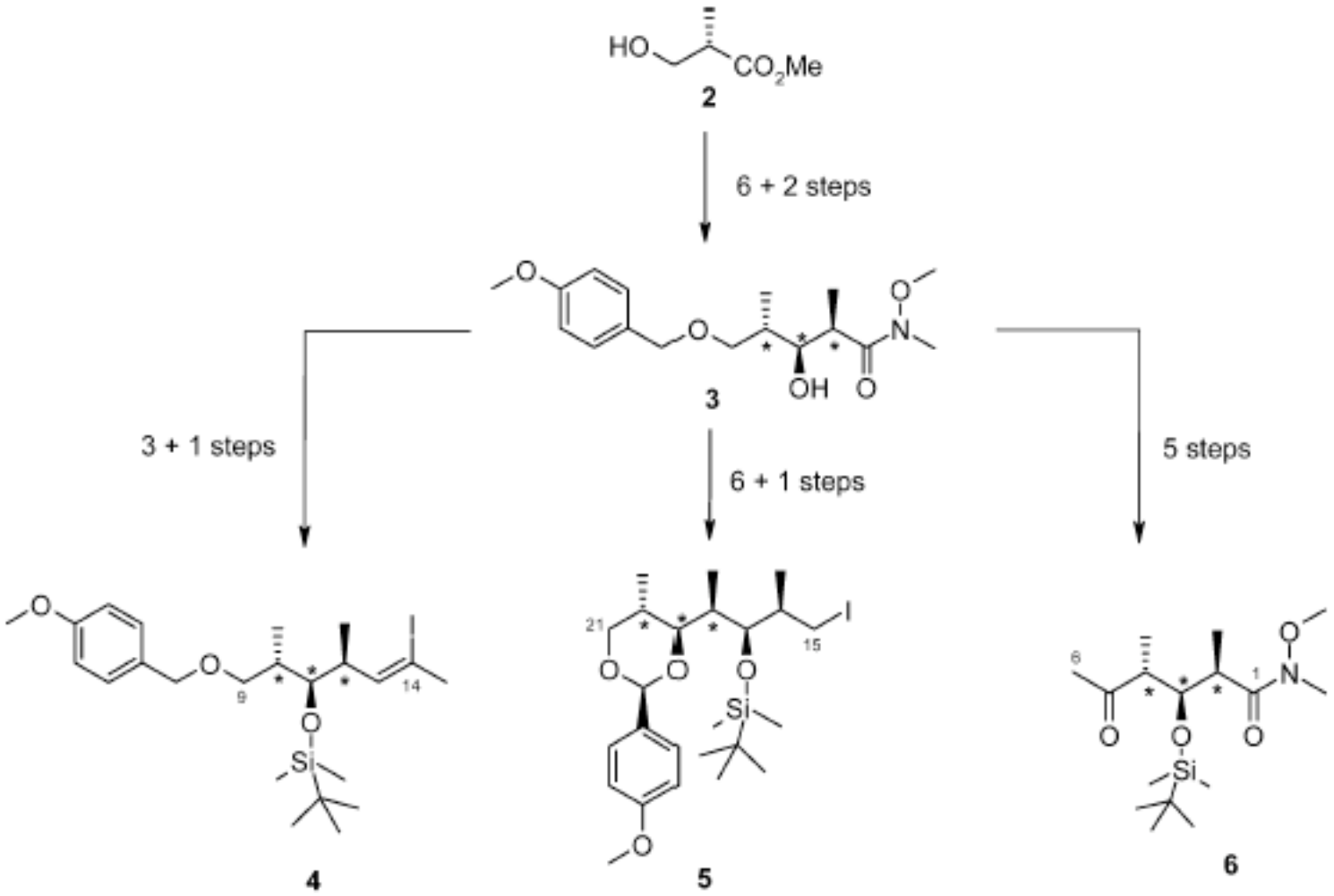
8→15: 2.78 kg of **8** was used; **15** was used immediately for next step due to its propensity for lactonization.

15→16: Used directly for next step; TEMPO: 2,2,6,6-tetramethylpiperidine-1-oxy radical.

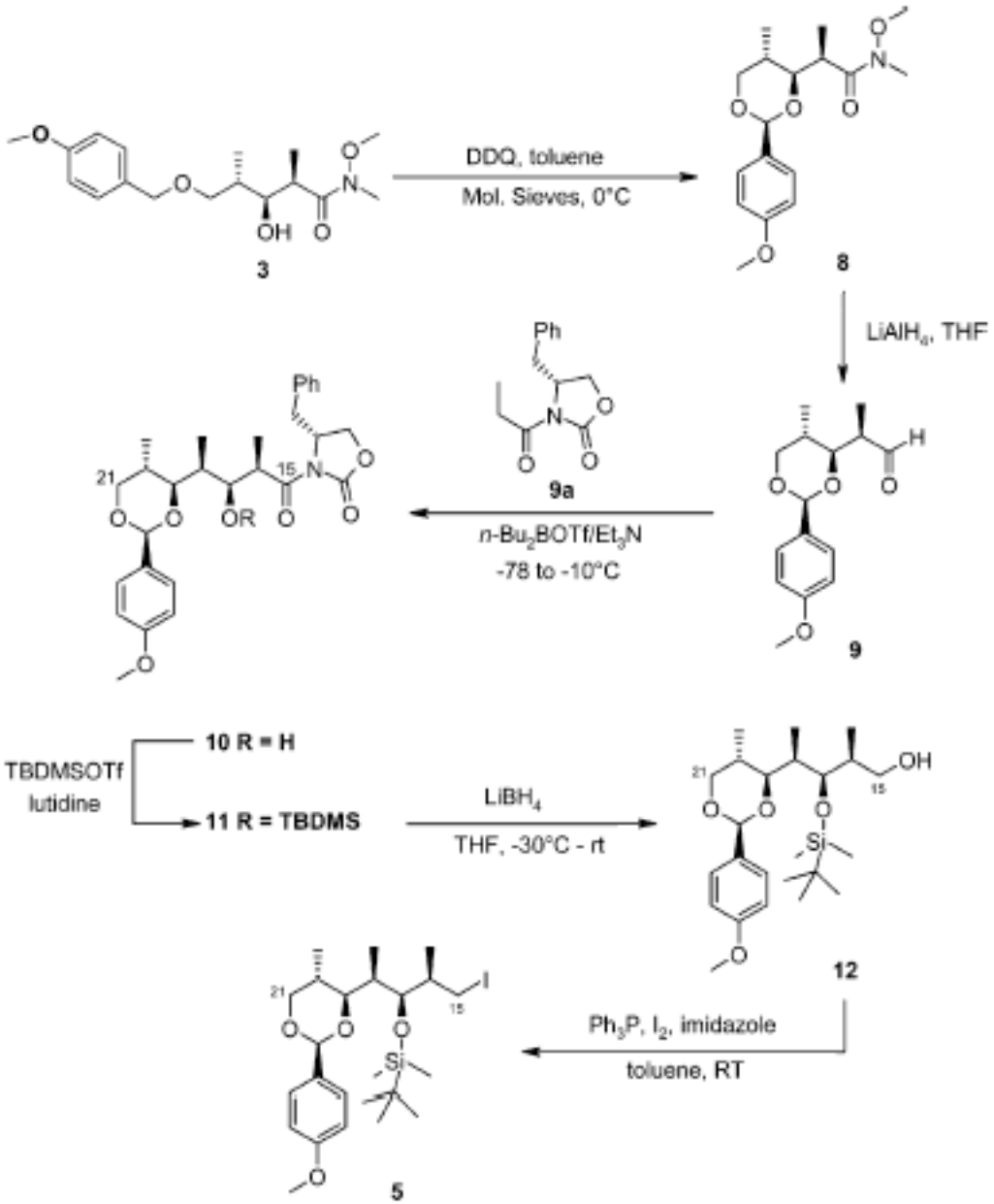
16→17: Used directly to minimize lactonization.

17→6: 1.26 kg, 66% yield (5 steps), by chromatography.

Synthesis of Fragment C15-21



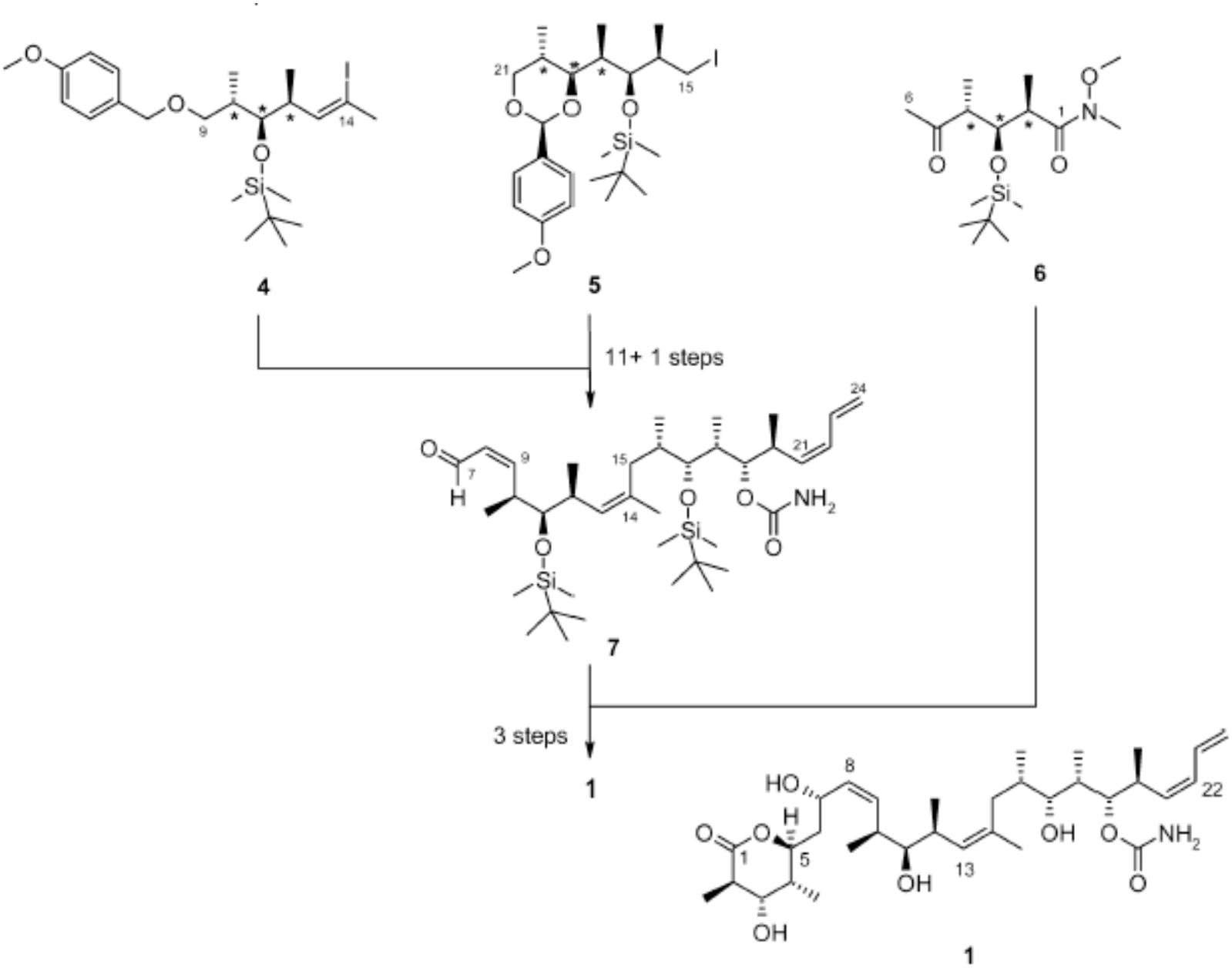
Synthesis of Fragment C15-21



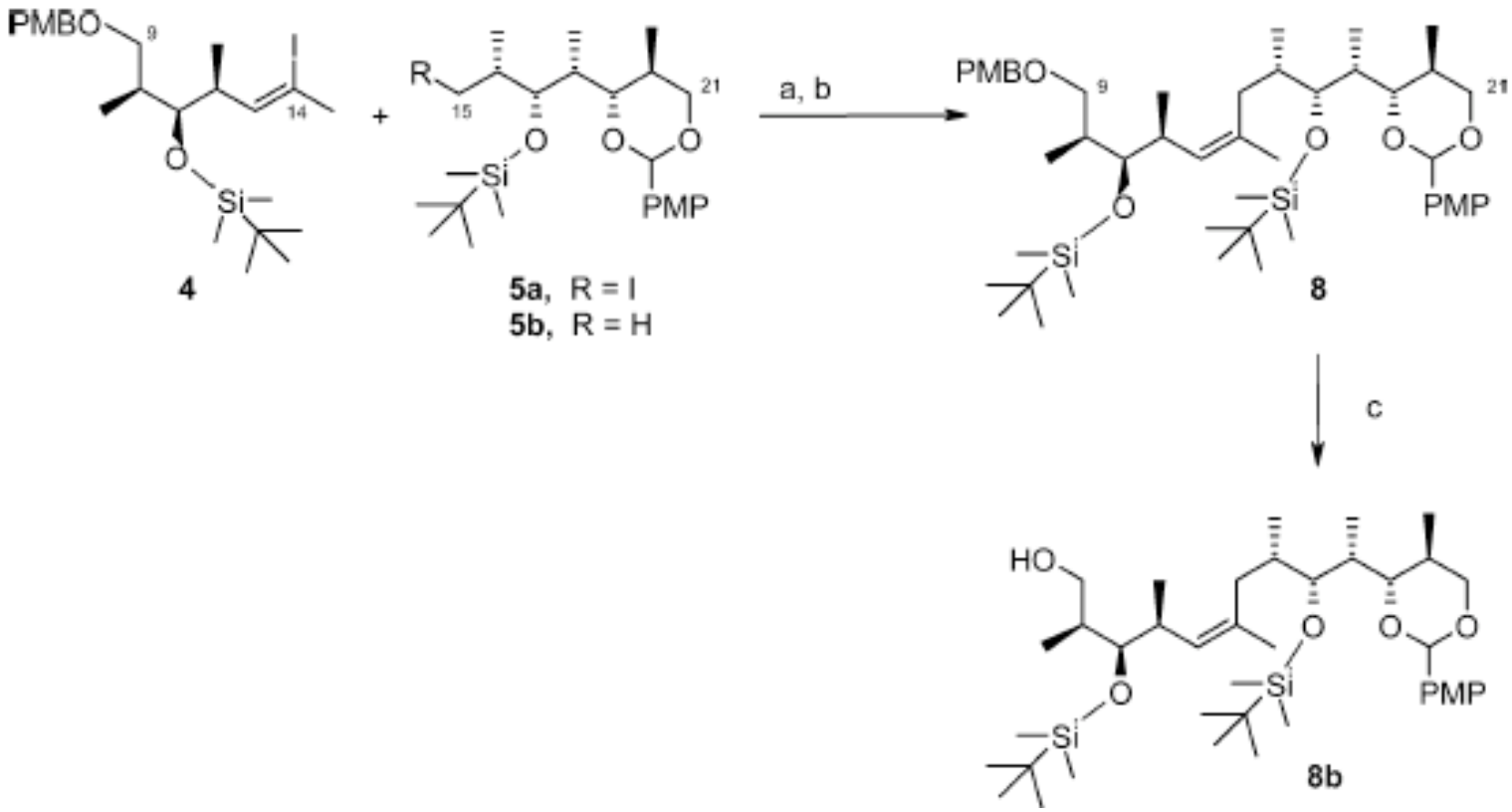
3→8: 61% by recrystallization.
8→9: 91% yield, controlled red.
9→10: 85% yield, temp < 0 °C.
High diastereomeric excess. **10** stable < -10 °C, otherwise, epimerization.
11→12: 60%, several byproducts.
12→5: 3.11 kg, 90% (chromatography).

Many crystalline intermediates!!

Synthesis of Fragment C7-24



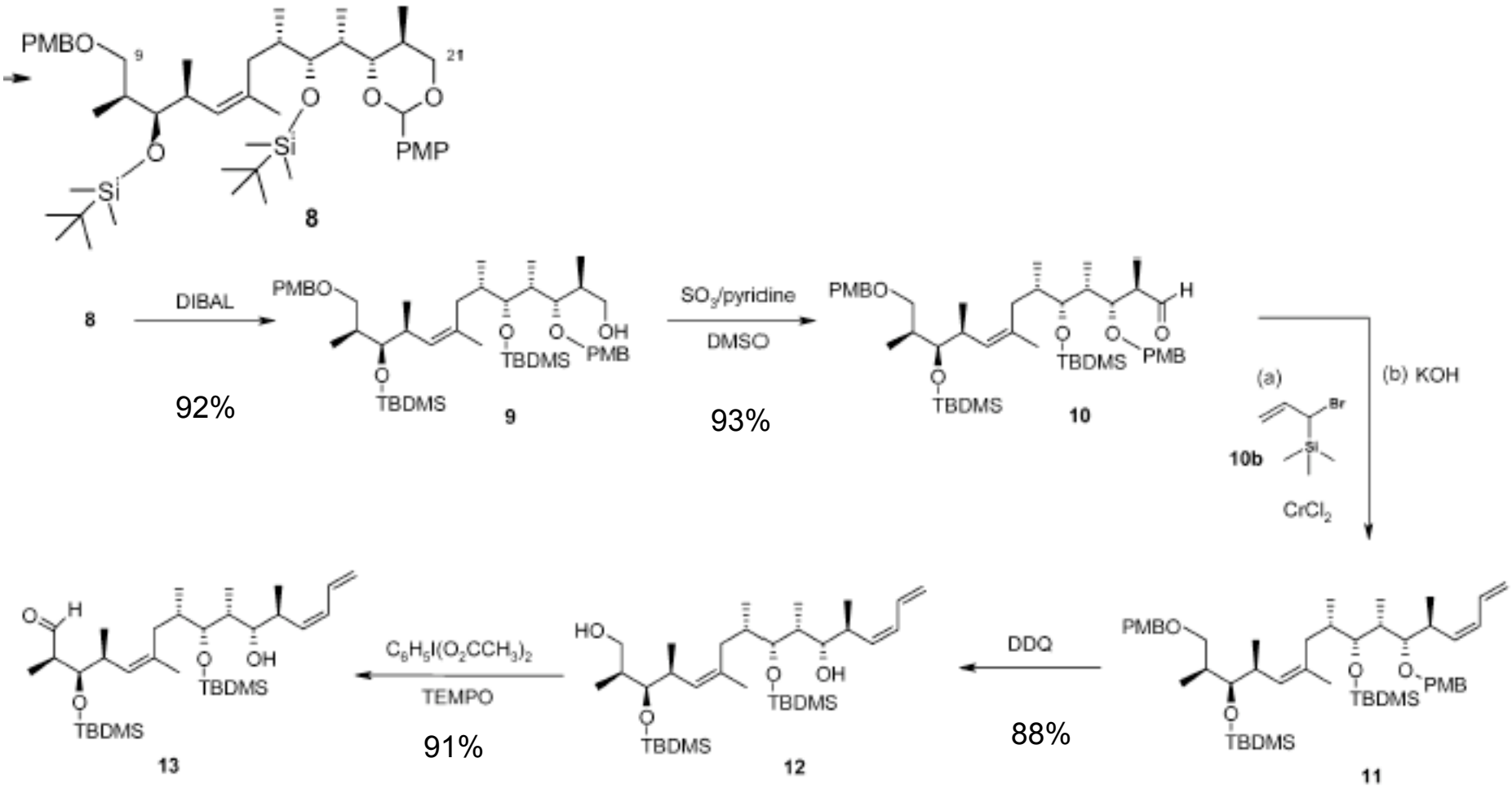
Coupling of 4 and 5



[a] Reagents: a) *t*-BuLi. 9-MeOBBN, THF, −78 °C; b) Cs_2CO_3, DMF, $Pd(dppf)_2Cl_2$, 20 °C; c) DDQ.

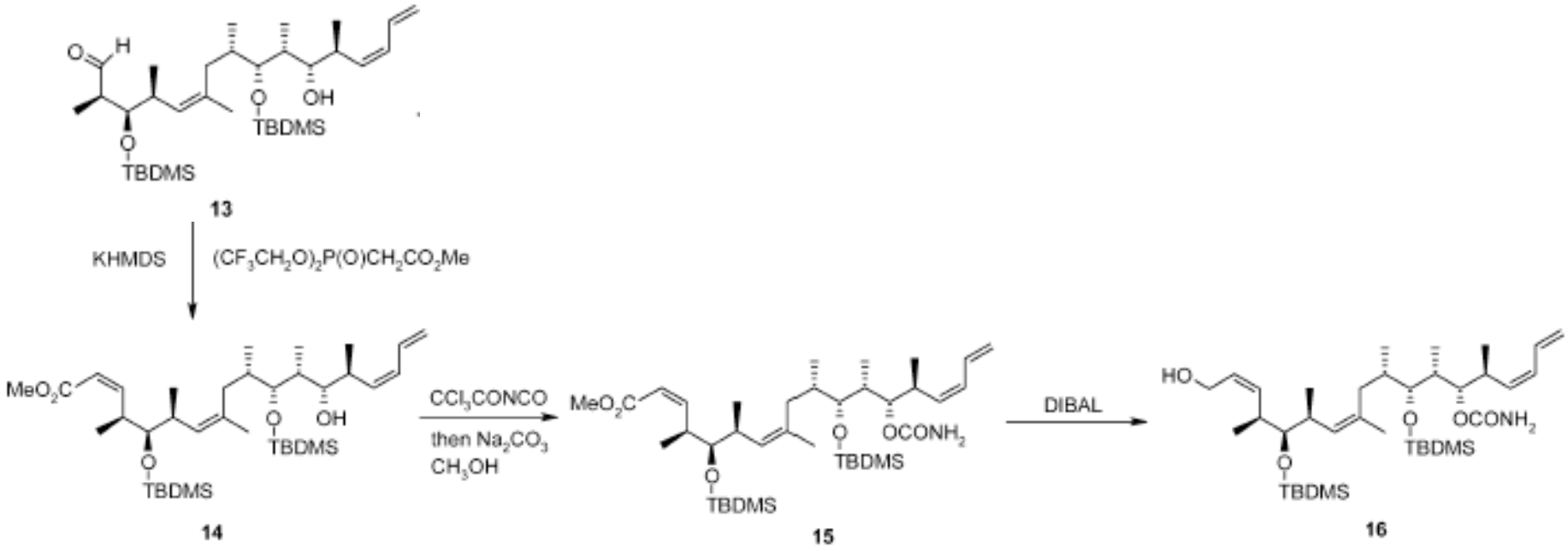
- Negishi coupling resulted in the formation of some inseparable side products, while Suzuki-type of cross-coupling used in Marshall's approach was bettter (73%).

Synthesis of C7-24 (7)



10→11: Nozaki-Hiyama allylation to form beta-hydroxysilane followed by syn-elimination. (Patterson's protocol), 81% yield.

Synthesis of C7-24 (7)

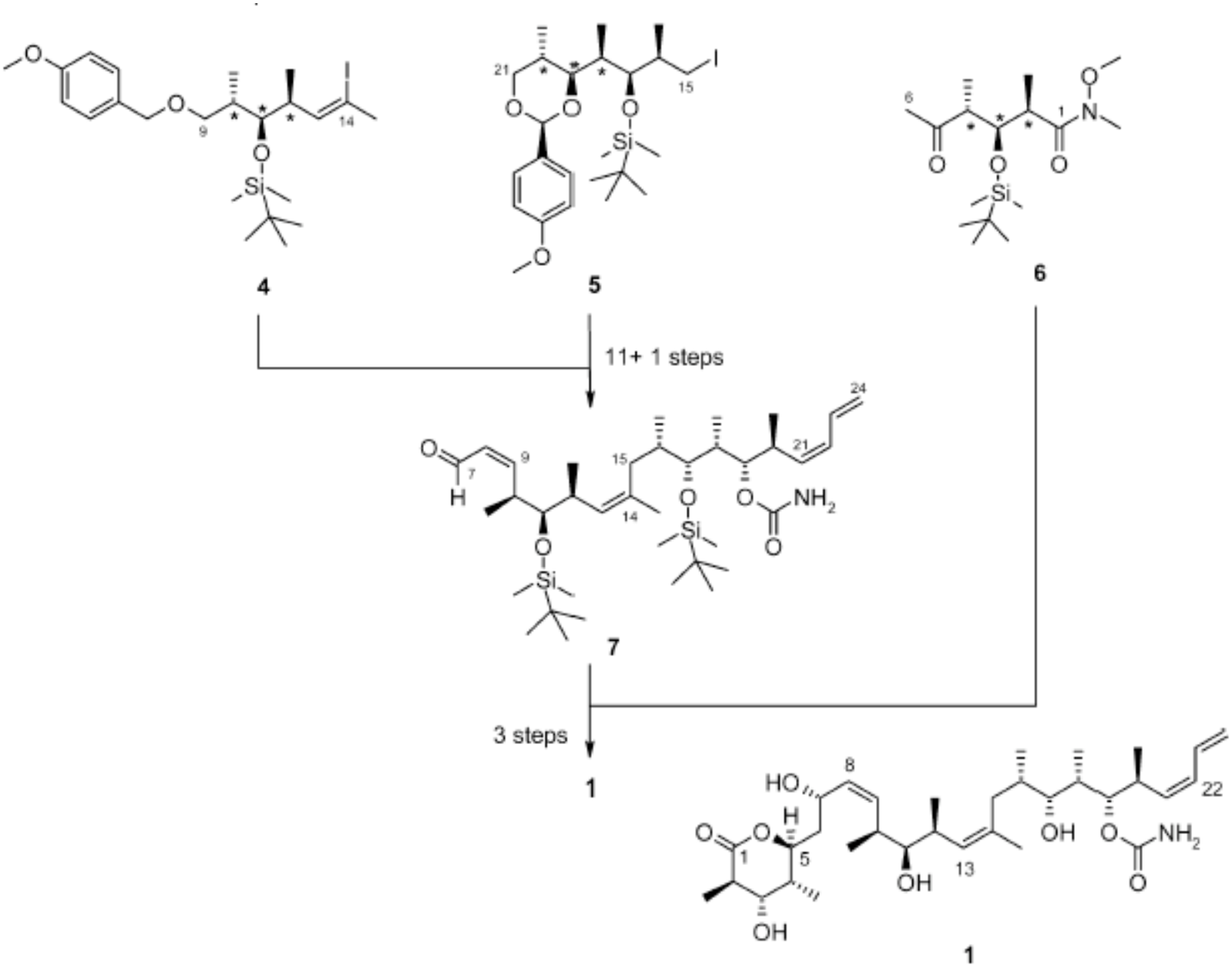


622 g, 76% yield (cis)

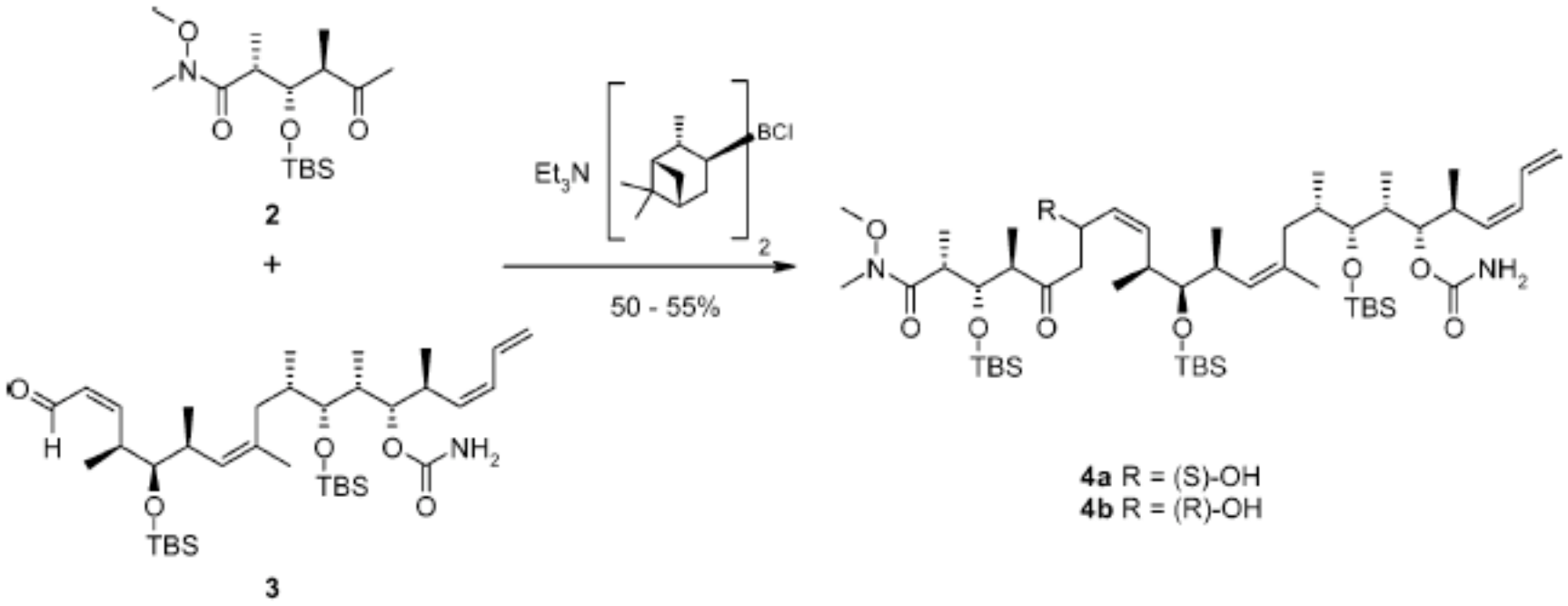
quantitive yield

647 g, 80% (two steps)

Finale (6 + 7)



Linkage of 6 and 7



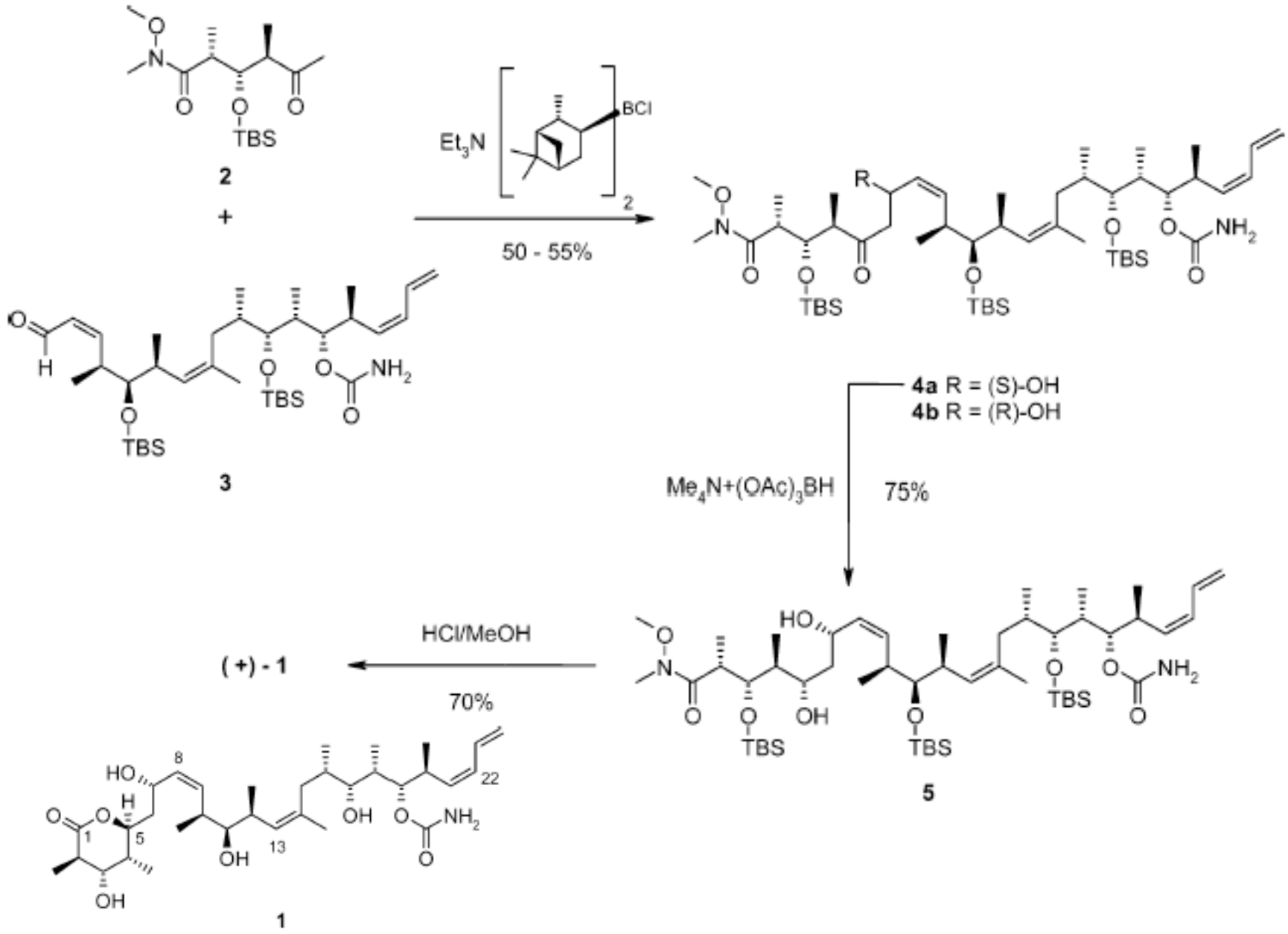
1. The quality of commercial (+)-DIP-Cl was capricious. The reagent problem was solved by utilizing a 70% solution of (+)-DIP-Cl in hexane. But still not good on scale-up.

2. Workup procedure? All these problems were overcome by simply omitting these workup steps.

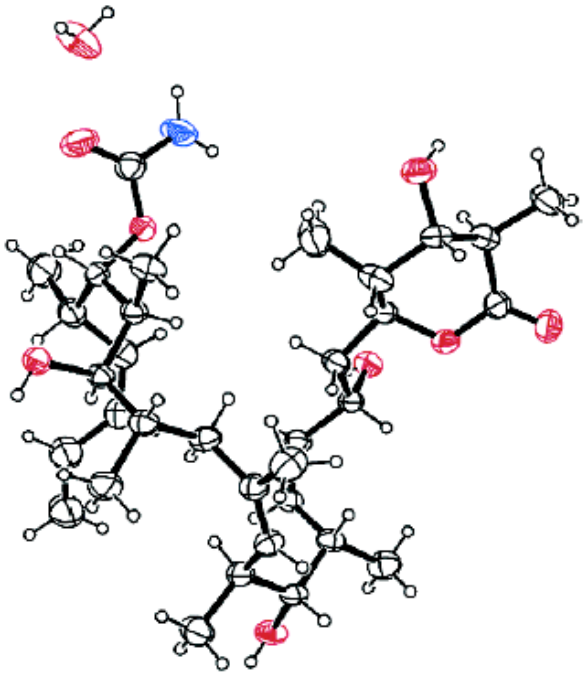
3. Finally, 50-55% yield in a reproducible manner.

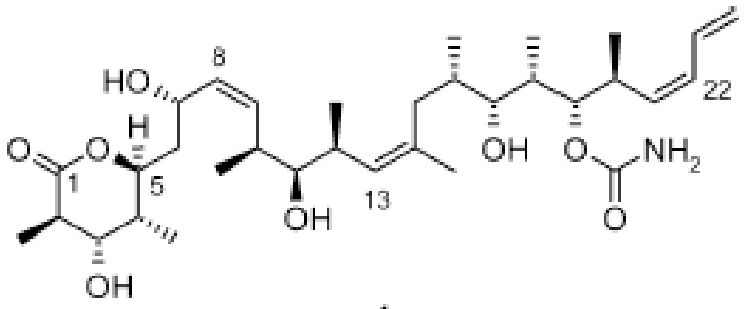
We certainly stumbled over this exact point during the final aldol coupling, and as a result the project very nearly ended in failure, or at least the required amount of discodermolide would not have been able to be delivered. But finally…

The End Game


2
+
3
Et3N
BCl
2
50 - 55%
4a R = (S)-OH
4b R = (R)-OH
Me4N+(OAc)3BH
75%
5
HCl/MeOH
70%
(+) - 1
1

(+)-Discodermolide





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1. Over 60 g of (+)-discodermolide was prepared in 39 steps and required 17 chromatographic purifications.
2. The majority of the steps were transferred to larger scale without any great problems.
3. Clearly, improving the yields of these problematic areas would be highly beneficial;
4. The end game is far from ideal; after such a synthetic sequence the final few steps leading to the final drug substance need to be kept "simple".
5. The entire process took some 20 months to complete. A total of over 43 chemists participated in the concept of the synthesis, experimental design, and execution.
6. The hybridized Novartis-Smith-Paterson synthetic route that resulted from this exercise is a crowning achievement to all those who participated in this endeavor.

“The Fruit”

Proof of synthesis

↓

Prep. of a 6-g batch

↓

Production of 60 g of (+)discodermolide

"The large-scale total synthesis of such a complex natural product in such quantities was a first for Novartis and probably the entire pharmaceutical industry." -- Stuart J. Mickel, Novartis

It's probably the best piece of synthetic work to come out from an industrial company. The ability to make something at this level of complexity as opposed to extracting it from natural product sources illustrates the power of modern synthetic chemistry." -- Steven Ley, Cambridge

"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, UPenn