

Literature Report



Enantioselective Synthesis of *des*-Epoxy-Amphidinolide N

Reporter: Mu-Wang Chen

Checker: Zi-Biao Zhao

Date: 2018-12-24

Trost, B. M.*; Bai, W.-J.; Stivala, C. E. *et al.*
J. Am. Chem. Soc. **2018**, *140*, 17316 - 17326.

CV of Prof. Trost, B. M.

Background:



- **1962** B.S., University of Pennsylvania
 - **1962-1965** Ph.D., Massachusetts Institute of Technology
 - **1965-1968** Assistant Professor, University of Wisconsin
 - **1968-1969** Associate Professor, University of Wisconsin
 - **1969-1987** Professor, University of Wisconsin
 - **1987-Now** Professor, Stanford University
-

Research:

- Designing new reactions and reagent involves the development of transition metal based catalysts.
- Developing new synthetic strategies towards complex natural products.

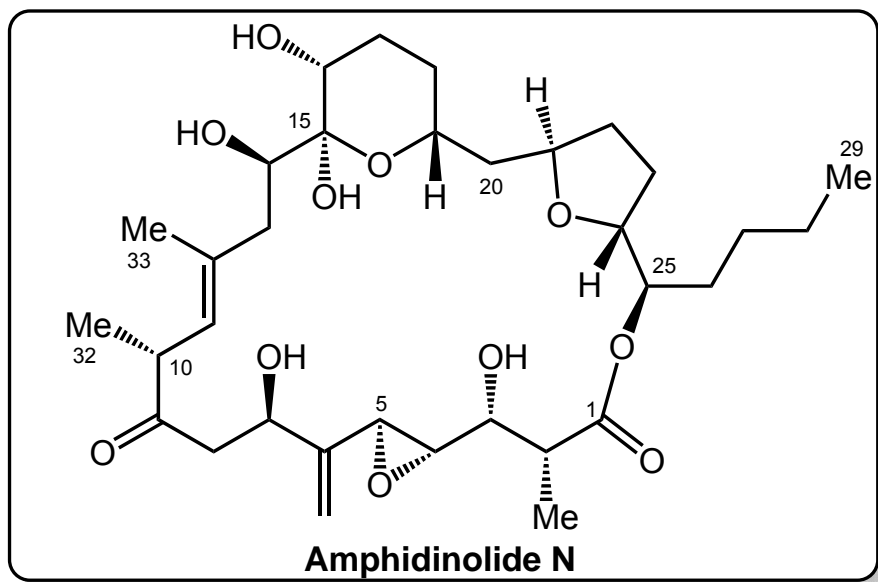
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2 Total Synthesis of *des*-Epoxy-Amphidinolide N

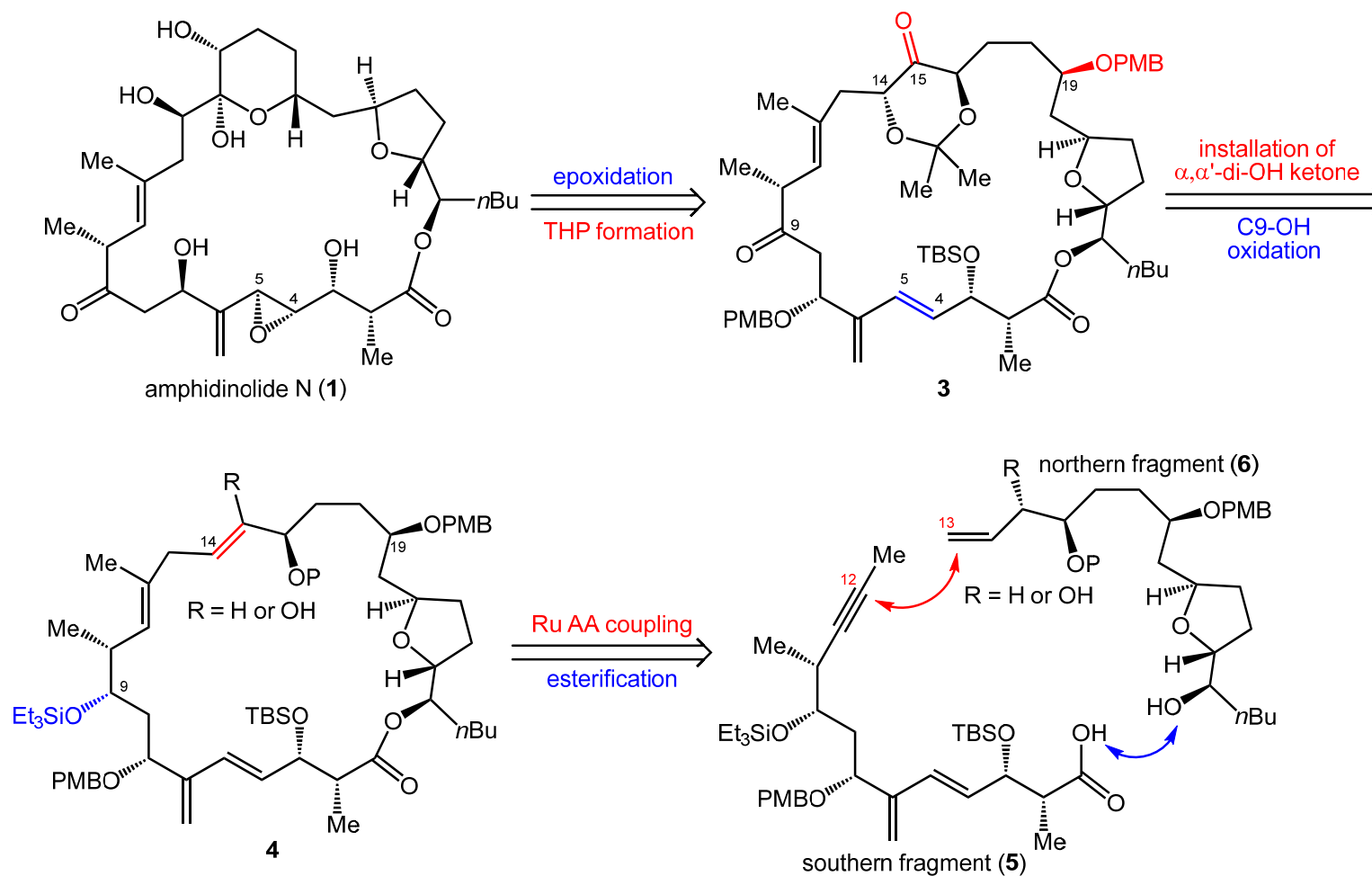
3 Summary

Introduction

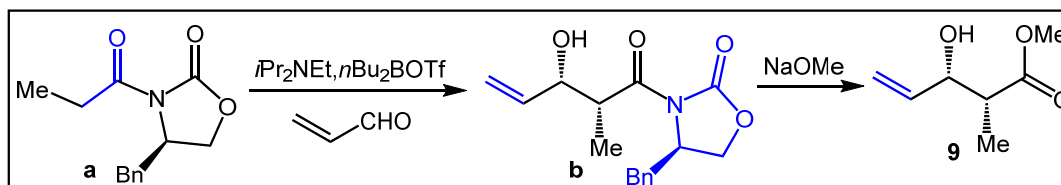
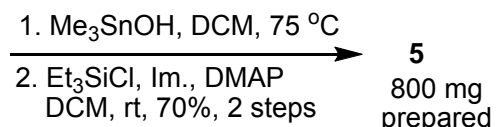
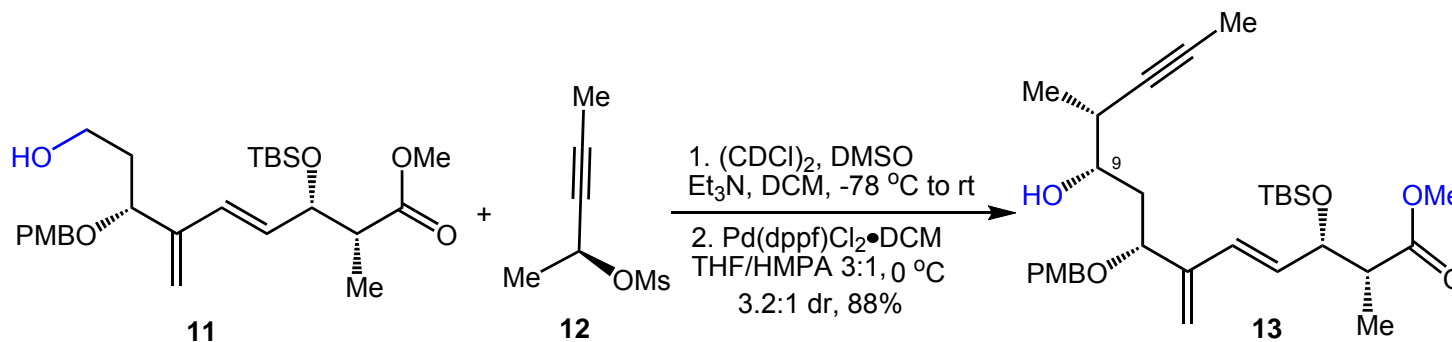
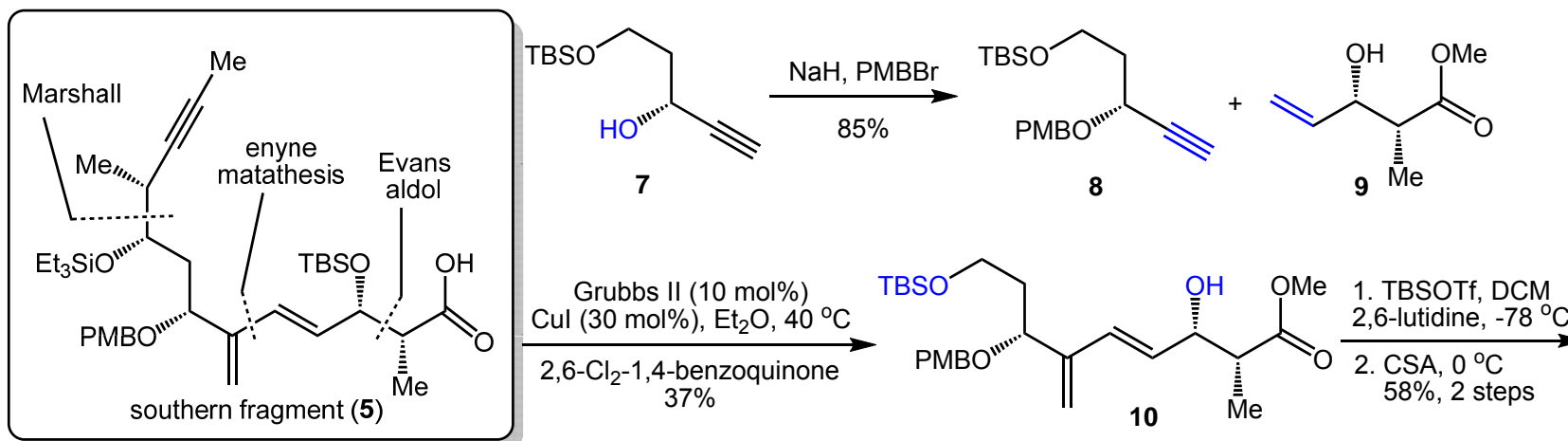


- Isolated from the symbiotic dinoflagellates of the genus *Amphidinium* in Okinawa;
- A complicated family member with a total of 13 stereocenters;
- Exhibit potent cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cell lines.

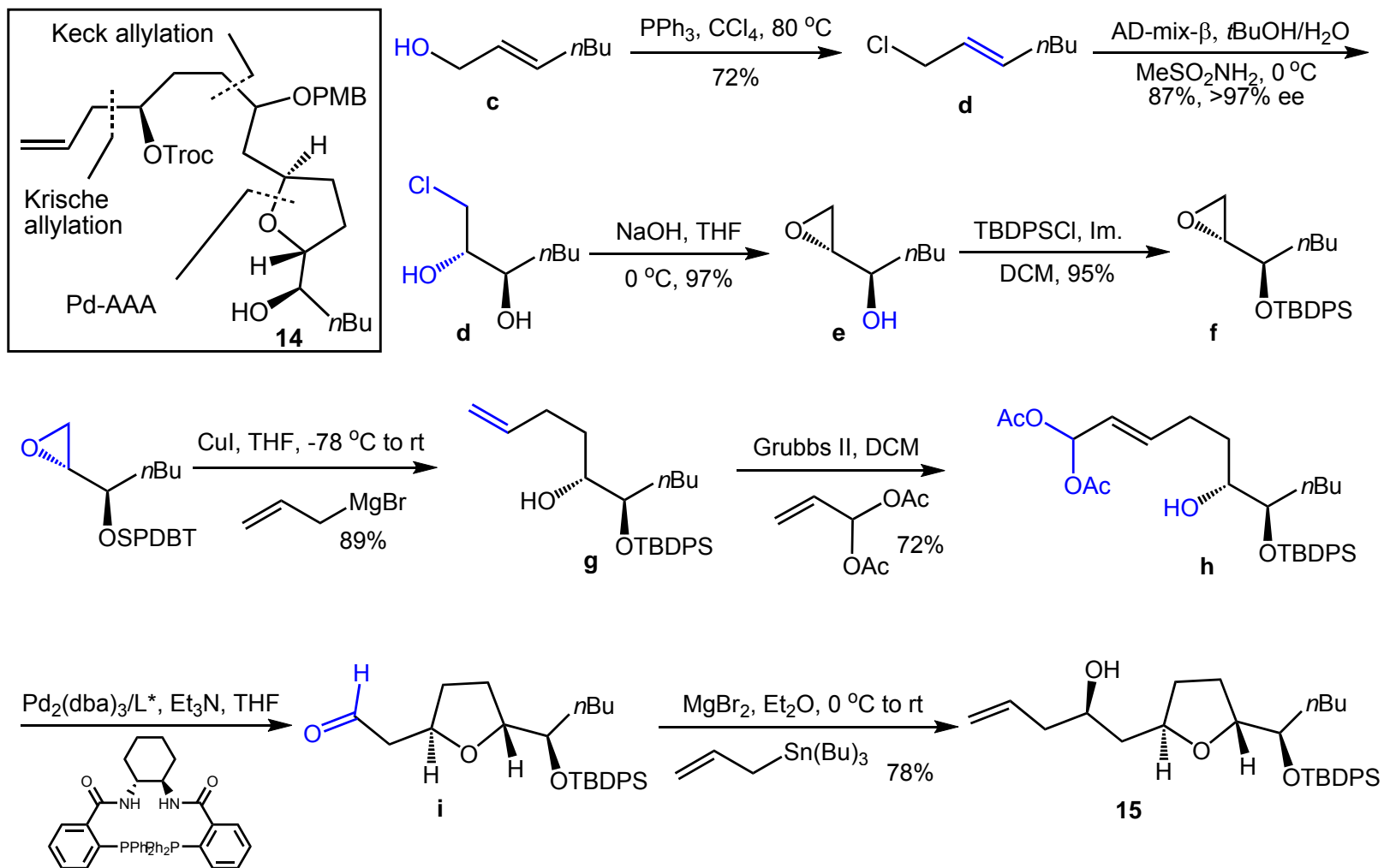
Retrosynthetic Analysis



Southern Fragment Synthesis (First Generation)

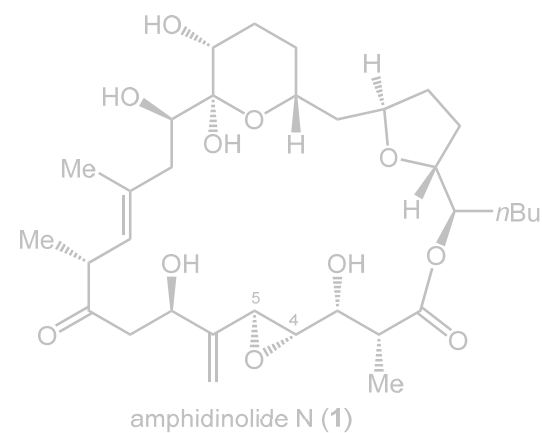
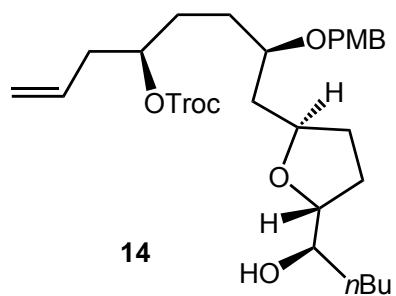
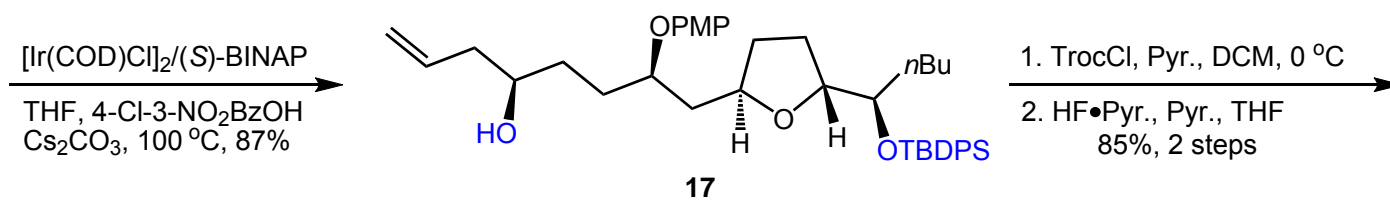
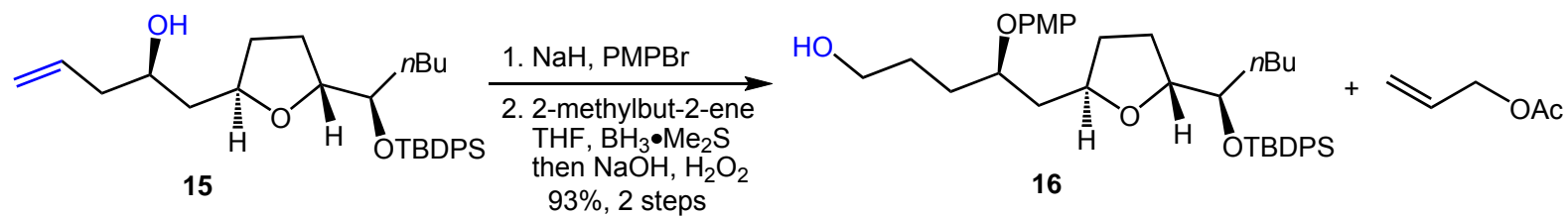


Northern Fragment Synthesis (First Generation)

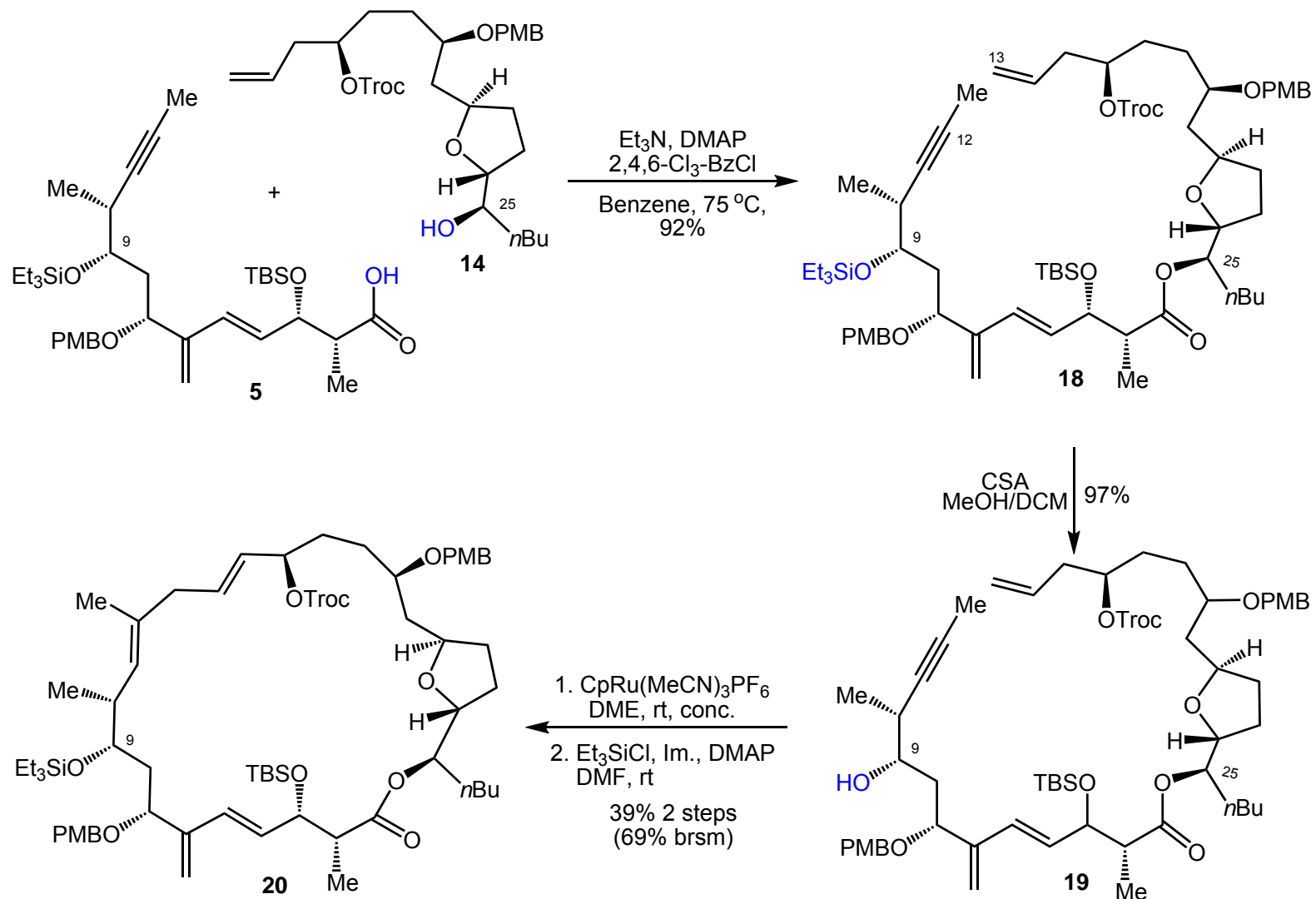


Trost, B. M.; Rey, J. *Org. Lett.* **2012**, *14*, 5632.

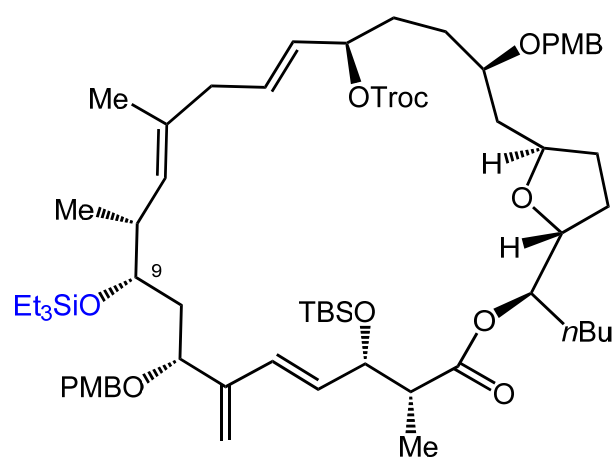
Northern Fragment Synthesis (First Generation)



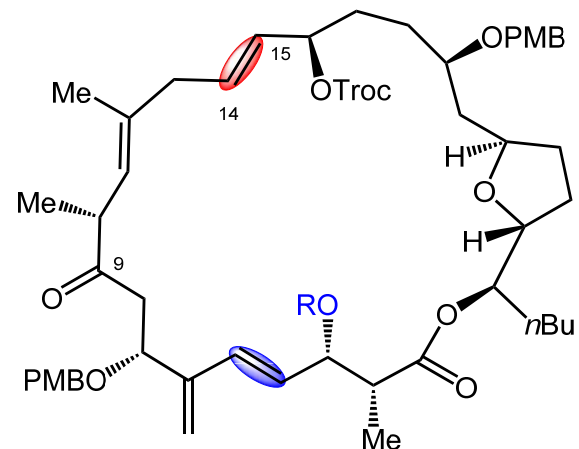
Assembly of the Southern and Northern Fragments (I)



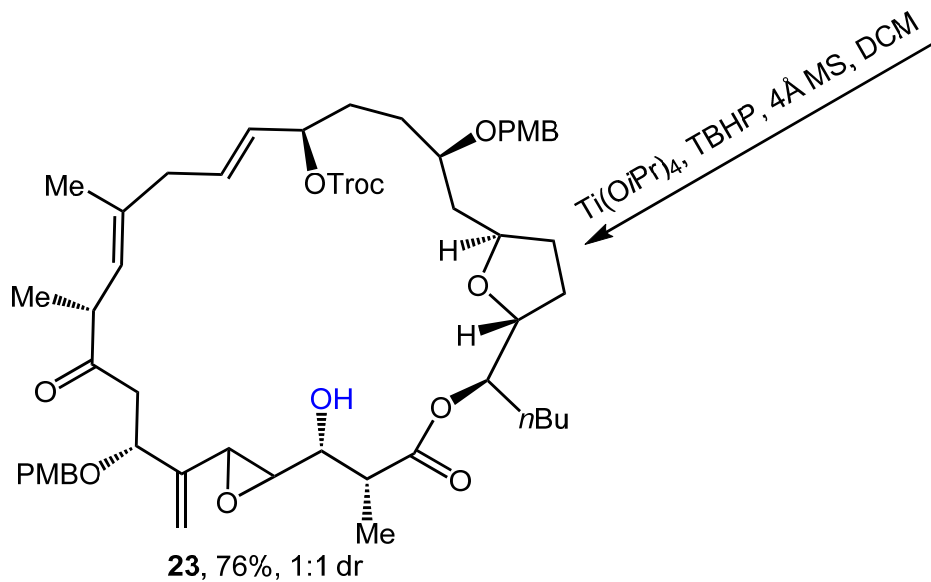
Assembly of the Southern and Northern Fragments (I)



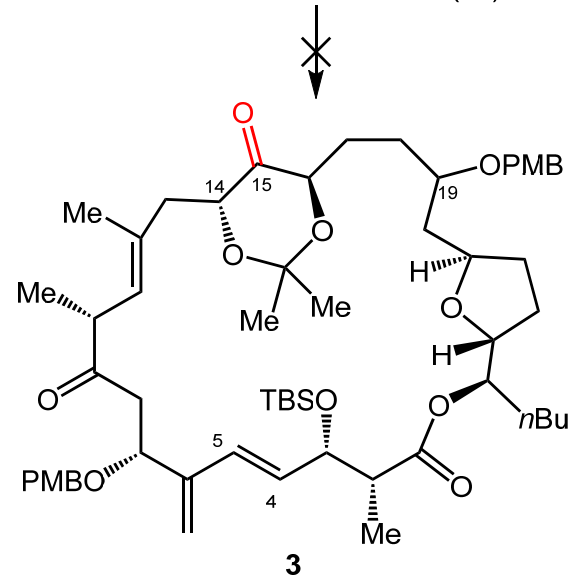
1. CSA, MeOH/DCM
2. DMP, Pyr., DCM
77%, 2 steps



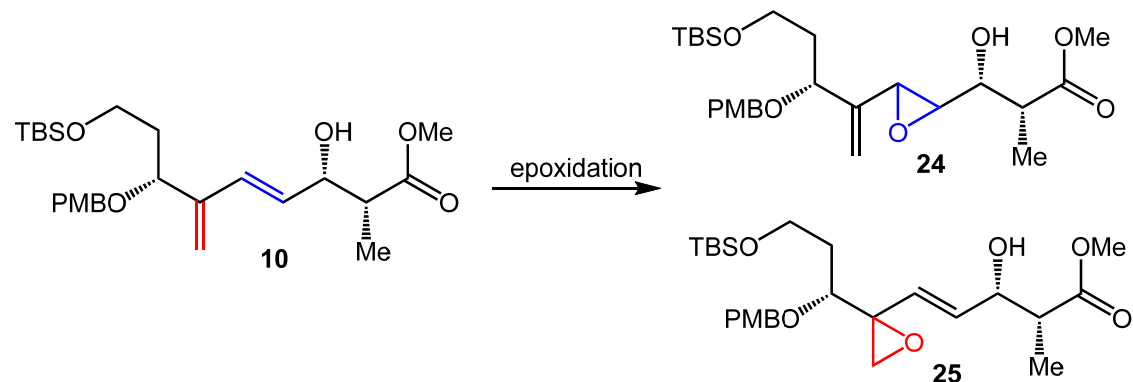
HF•Pyr
THF, 89%
R = TBS (21)
R = H (22)



Ti(OiPr)₄, TBHP, 4Å MS, DCM

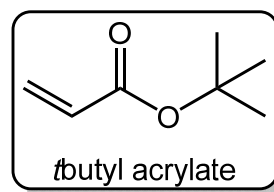
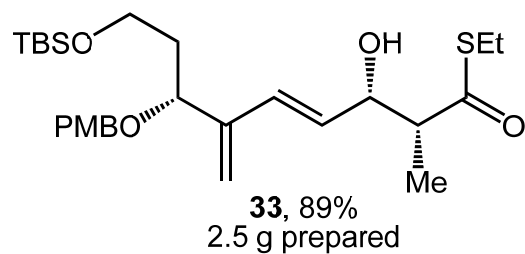
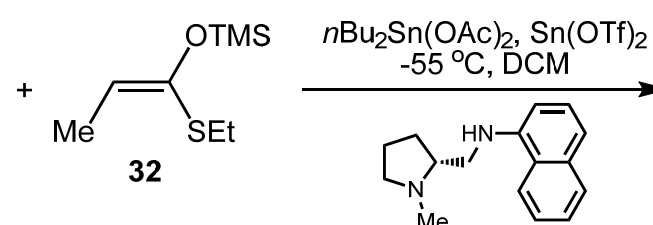
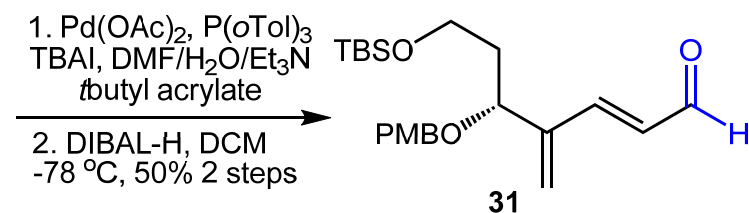
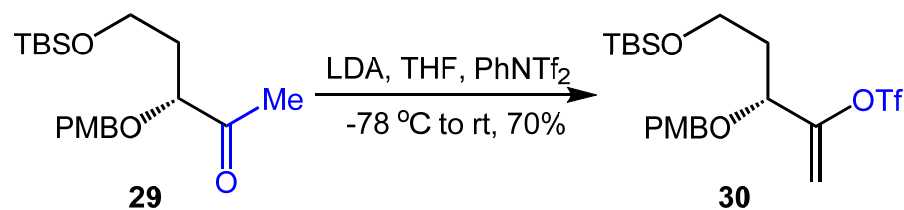
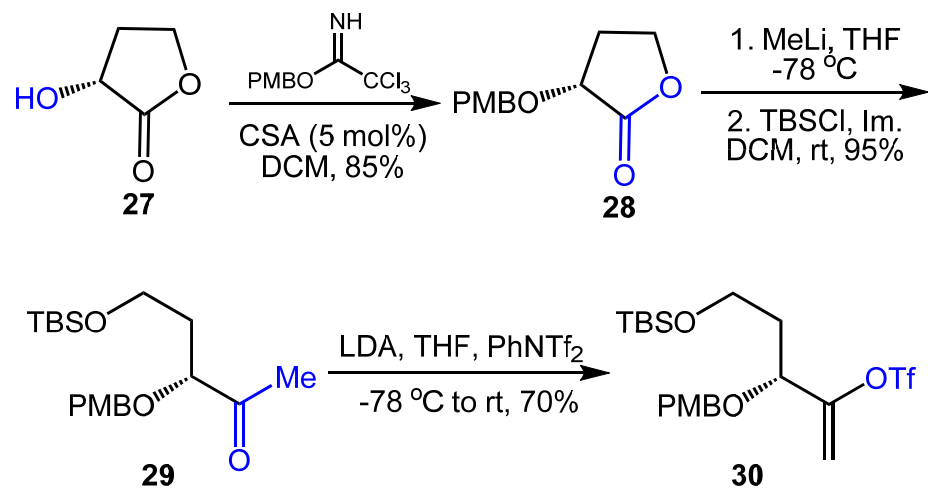
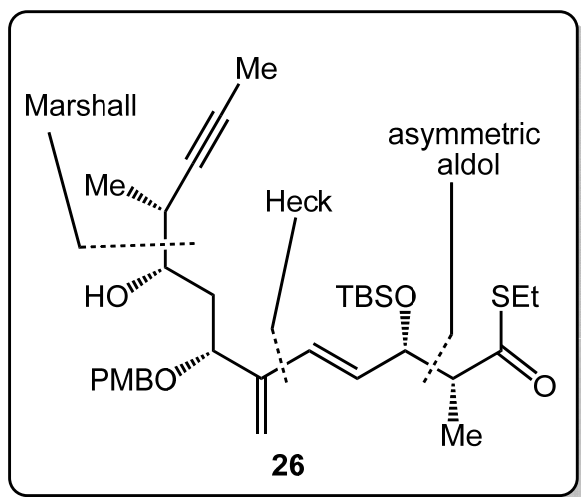


Epoxidation of Diene 10

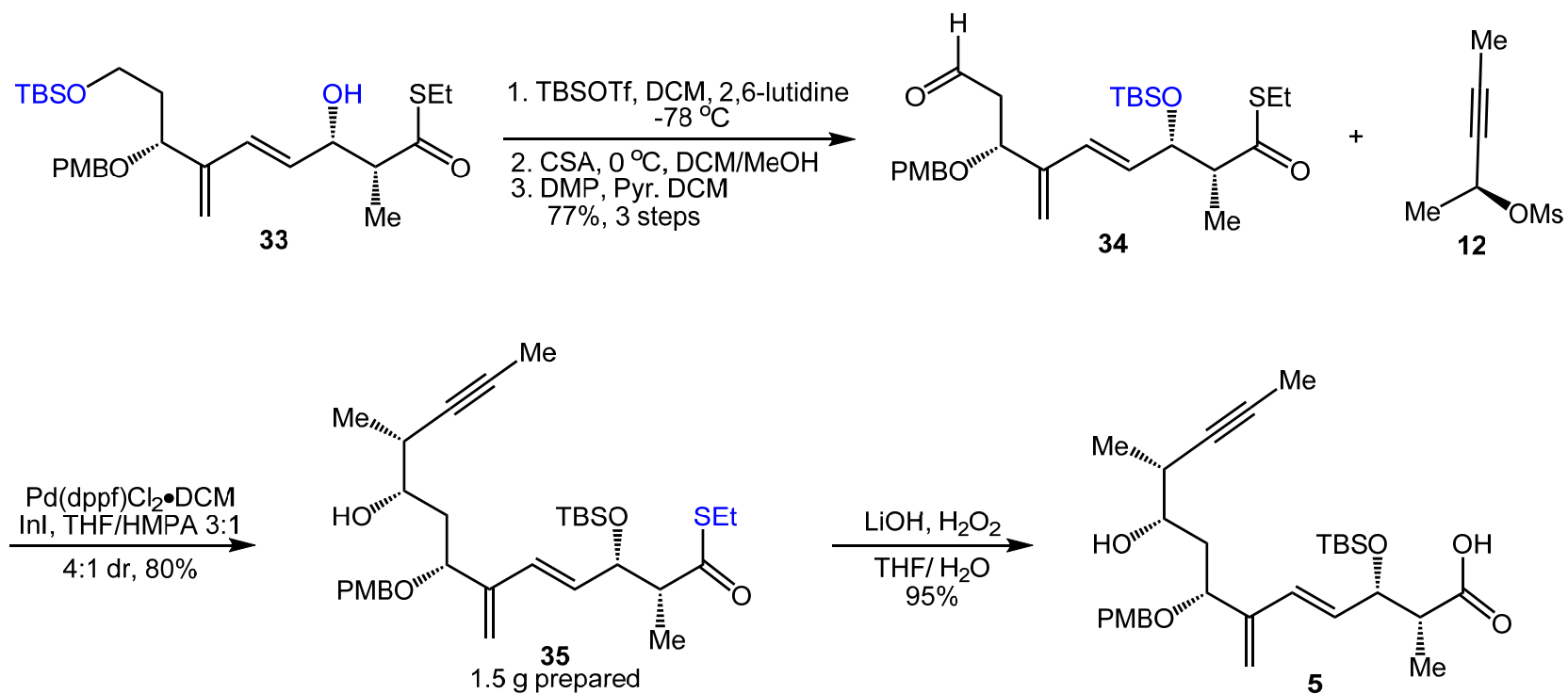


entry	coditions	conv ^b	24:25 ^b	dr (24) ^b
1	DMDO	100%	0:100	N/A
2	<i>m</i> CPBA	100%	91:9	1.6:1
3	Ti(O ^{<i>i</i>} Pr) ₄ , TBHP, 4Å MS	100%	100:0	3:1
4	VO(acac) ₂ , TBHP, 5Å MS	100%	100:0	>1:20
5	3,5-di(CF ₃)-benzoxitrile H ₂ O ₂ , KHCO ₃	72	88:12	6:1

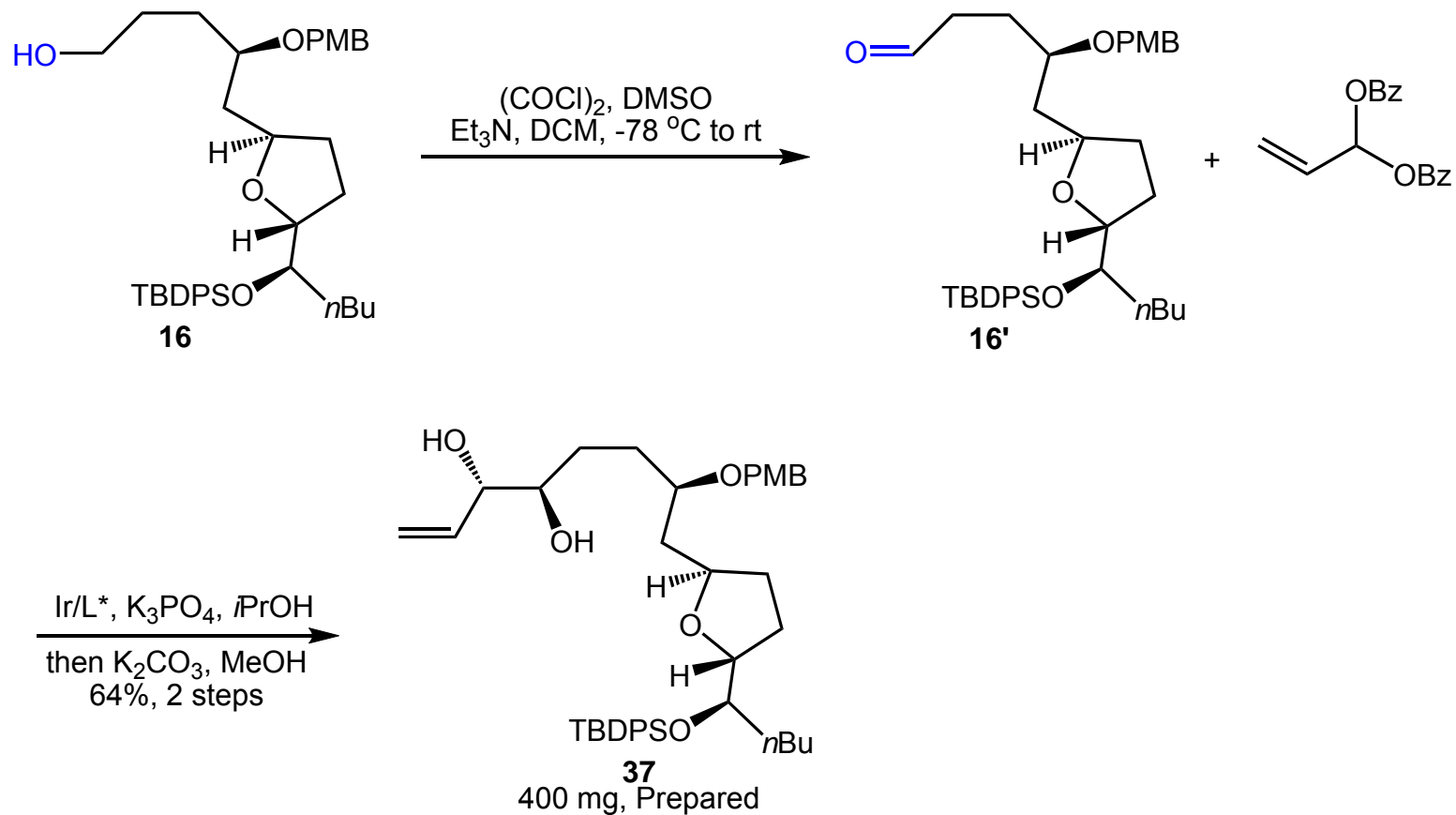
Southern Fragment Synthesis (Second Generation)



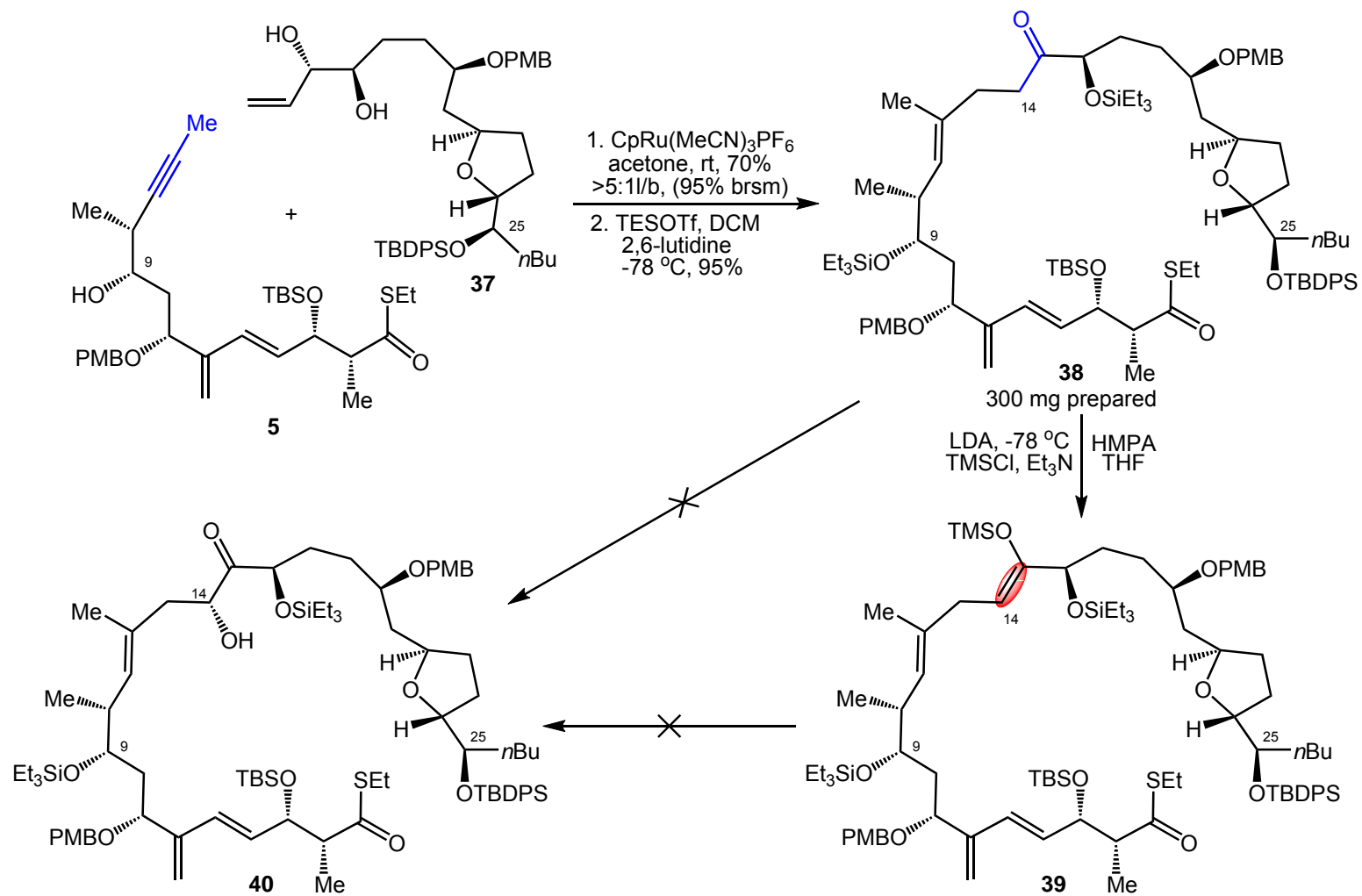
Southern Fragment Synthesis (Second Generation)



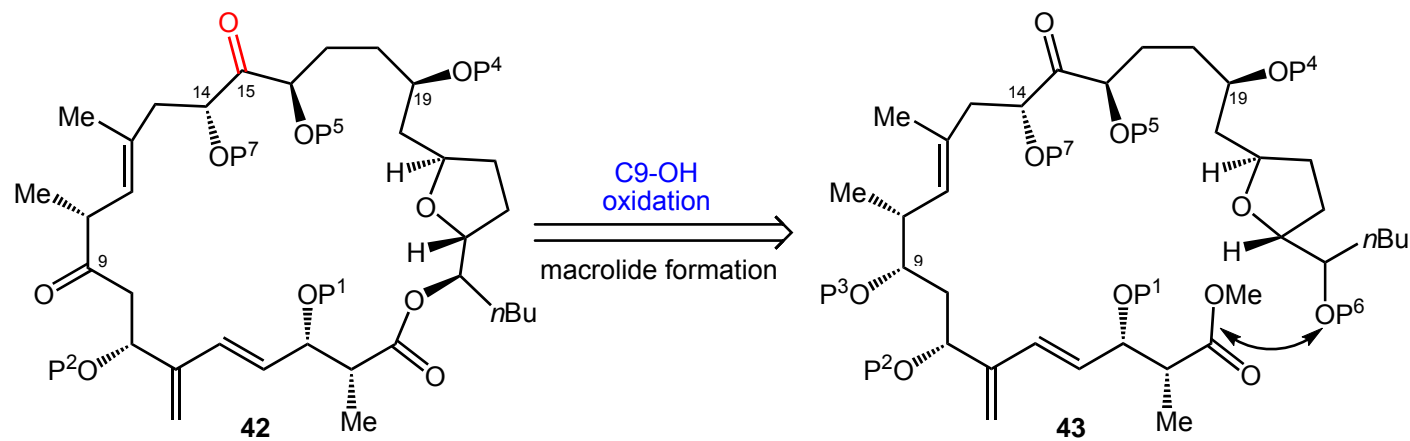
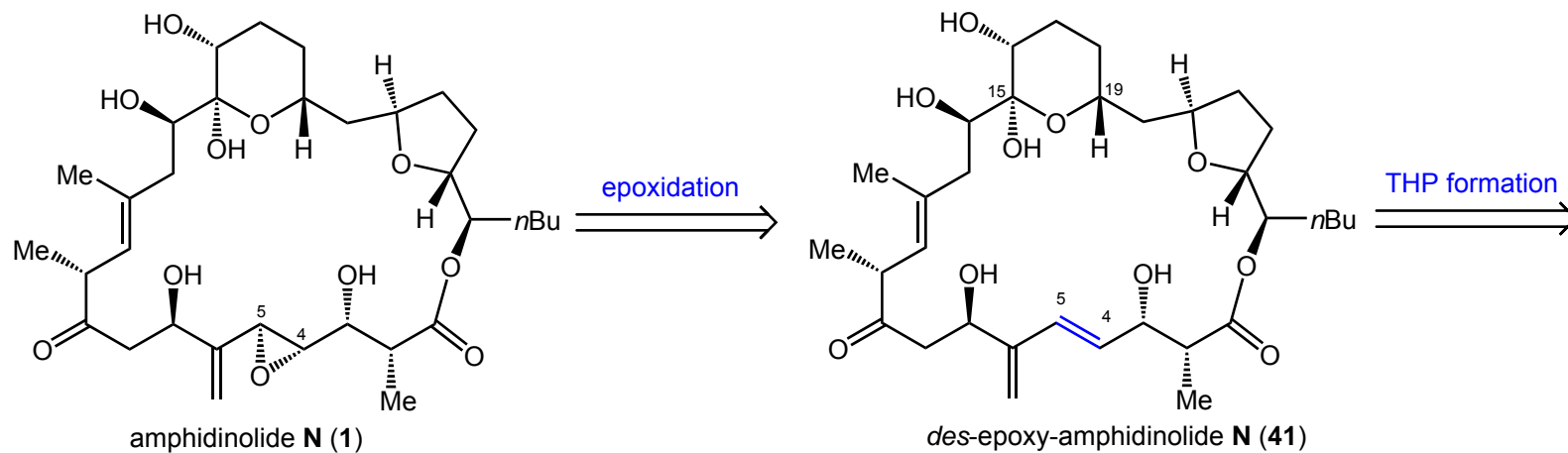
Northern Fragment Synthesis (Second Generation)



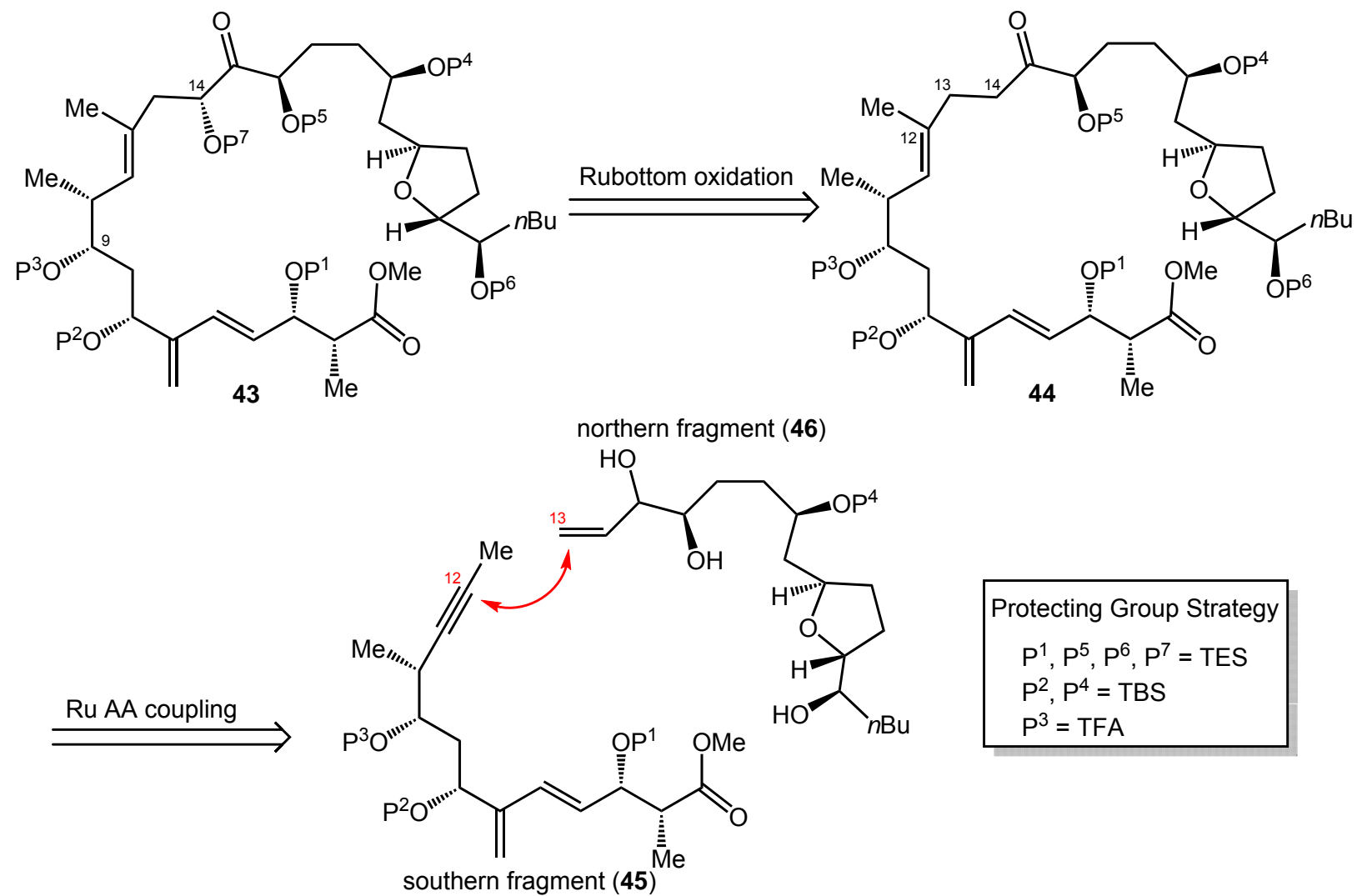
Assembly of the Southern and Northern Fragments (II)



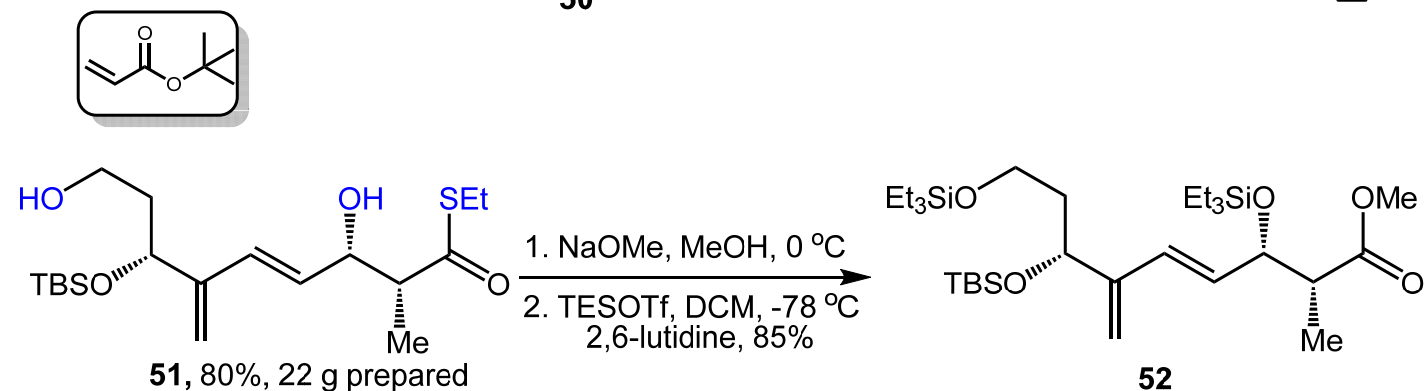
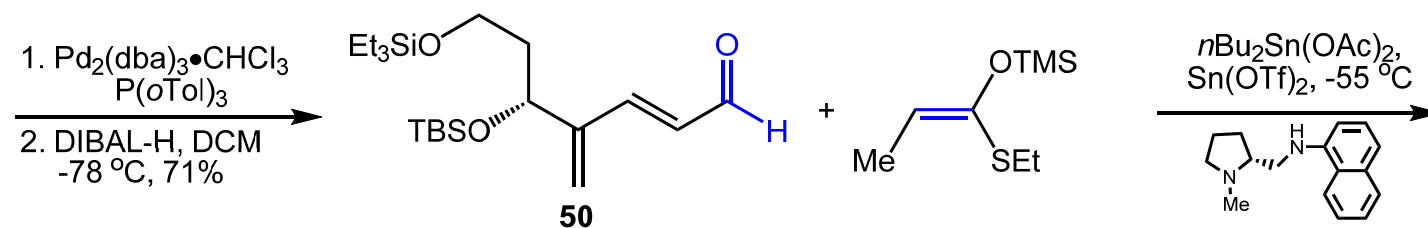
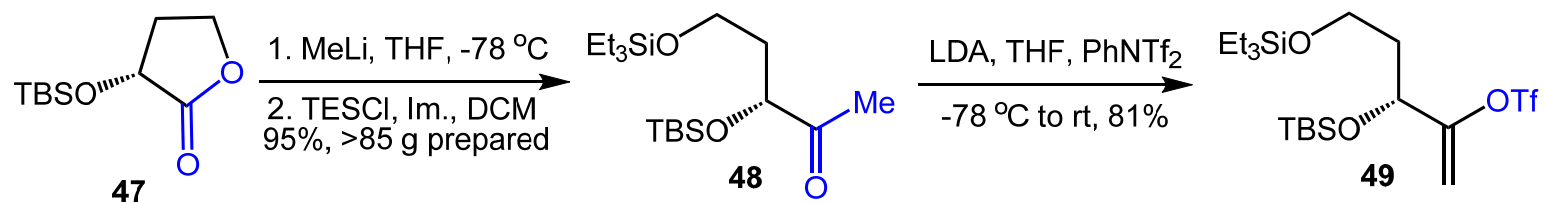
Highlighting a Judicious Protecting Group Strategy



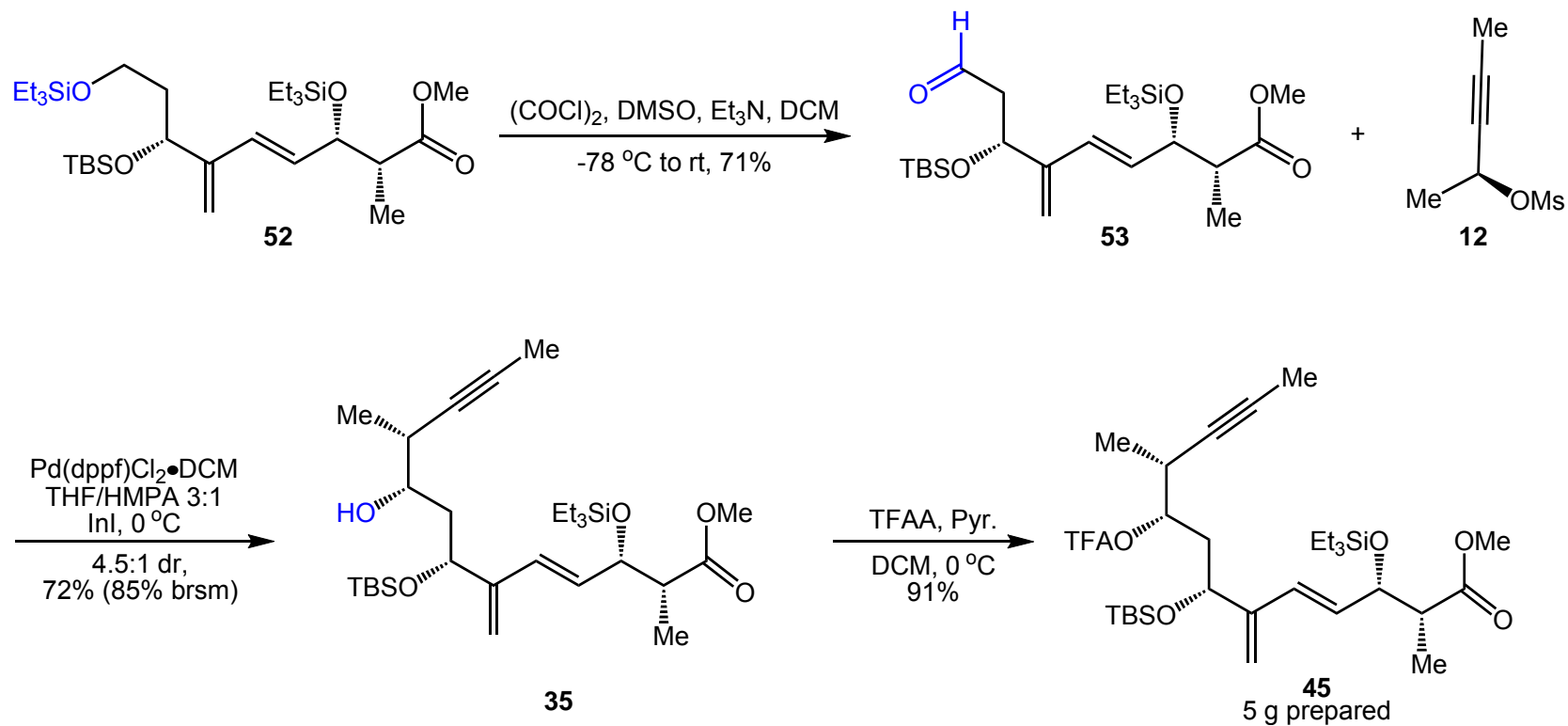
Highlighting a Judicious Protecting Group Strategy



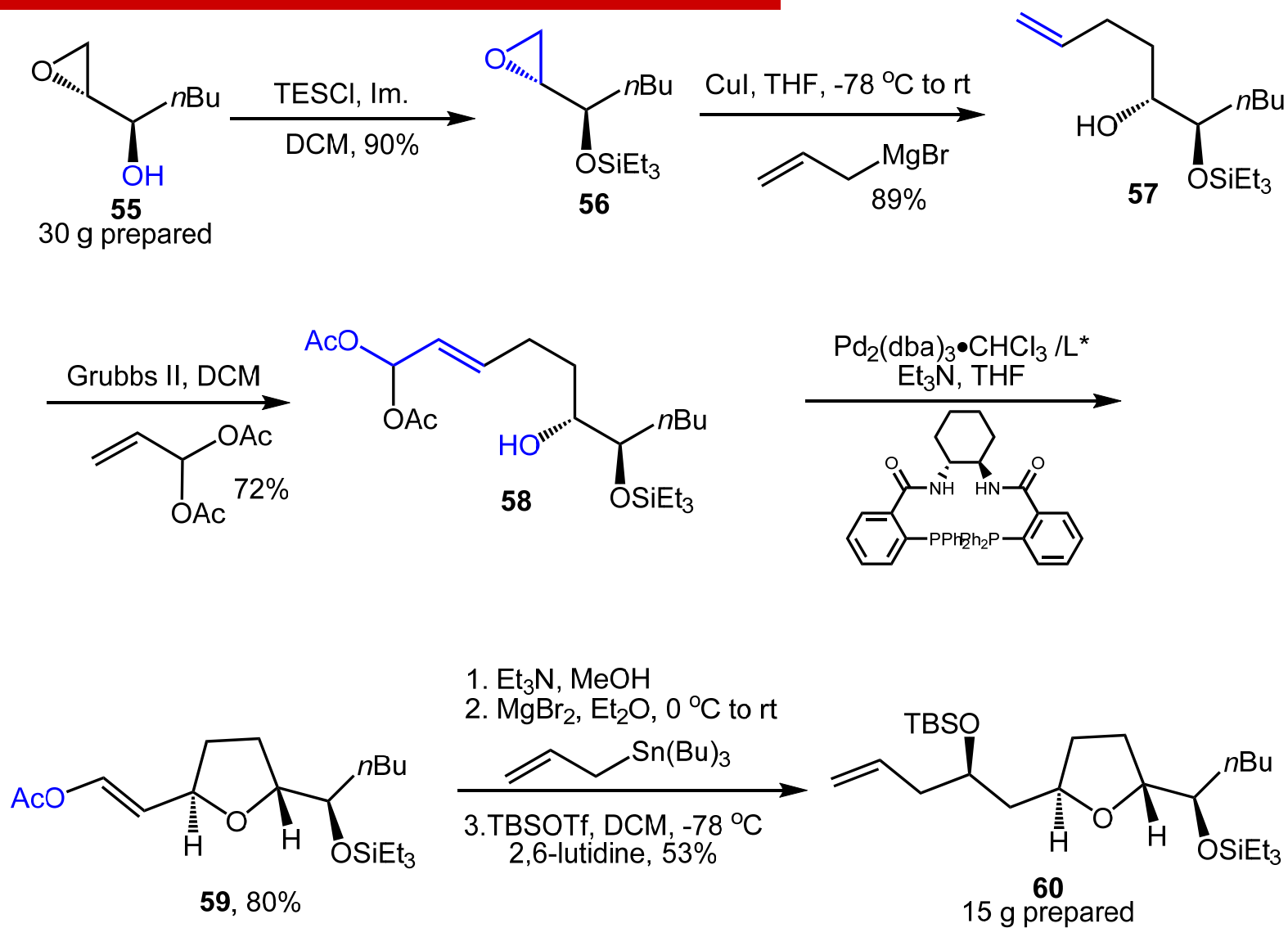
Southern Fragment Synthesis (Final Generation)



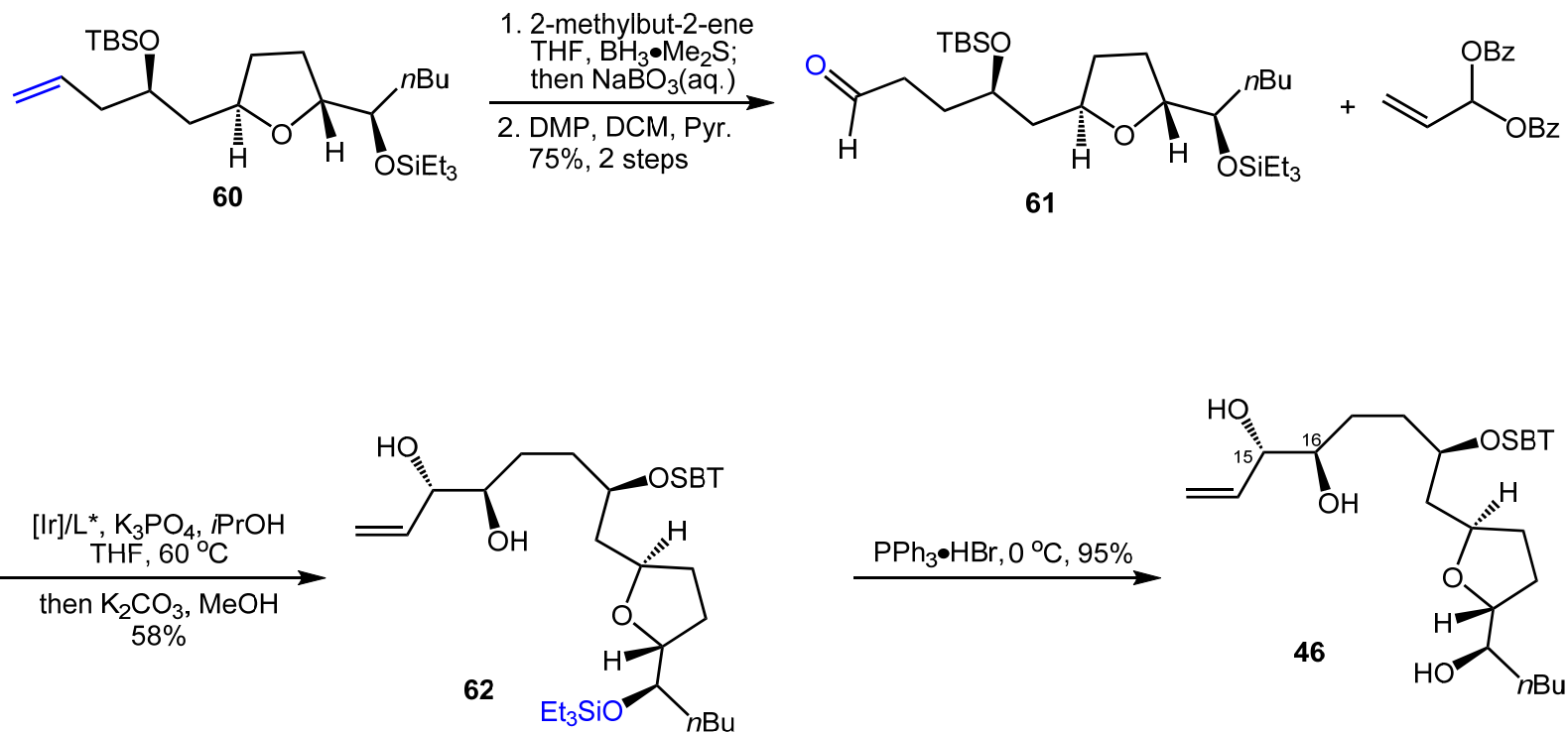
Southern Fragment Synthesis (Final Generation)



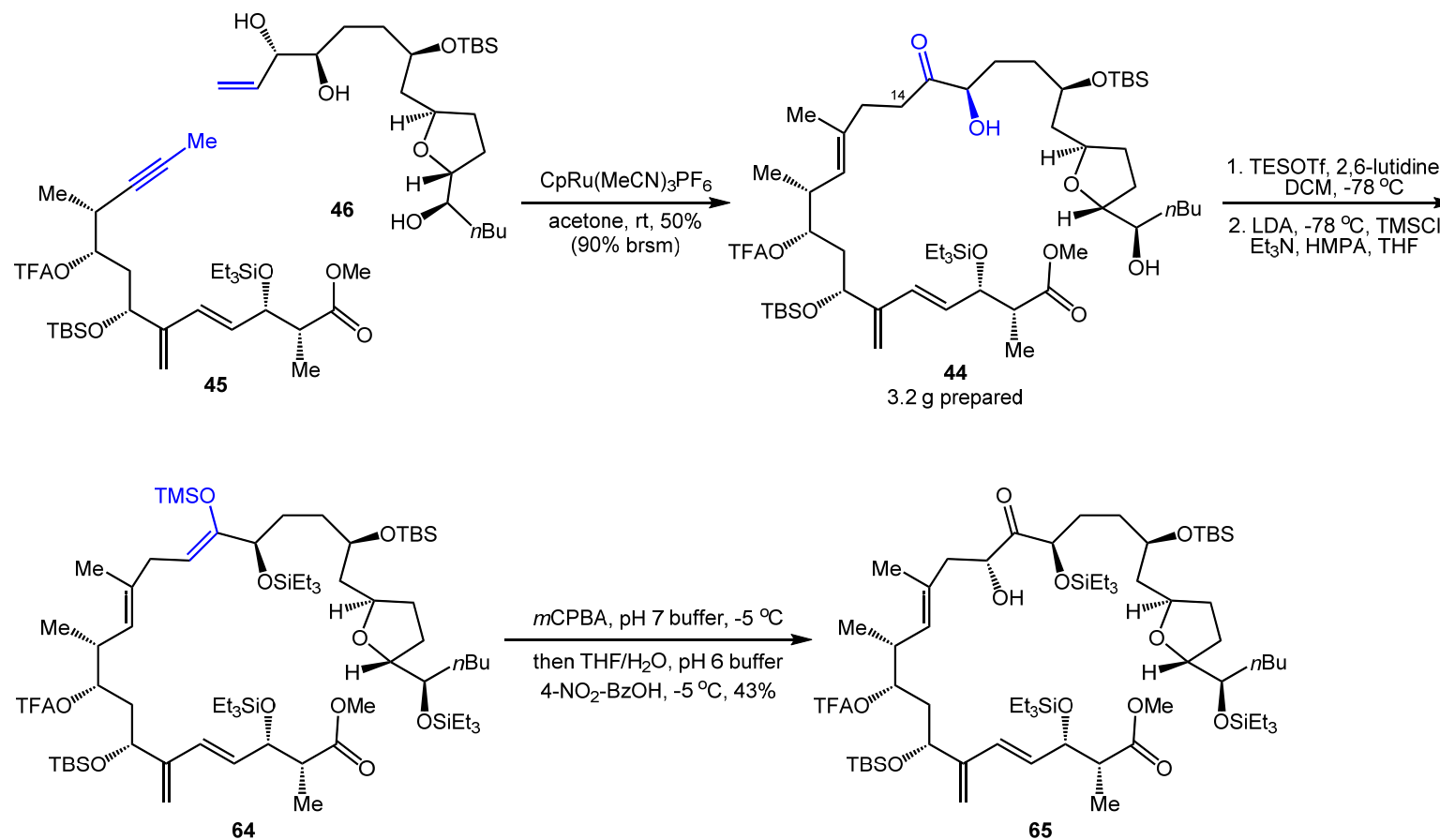
Northern Fragment Synthesis (Final Generation)



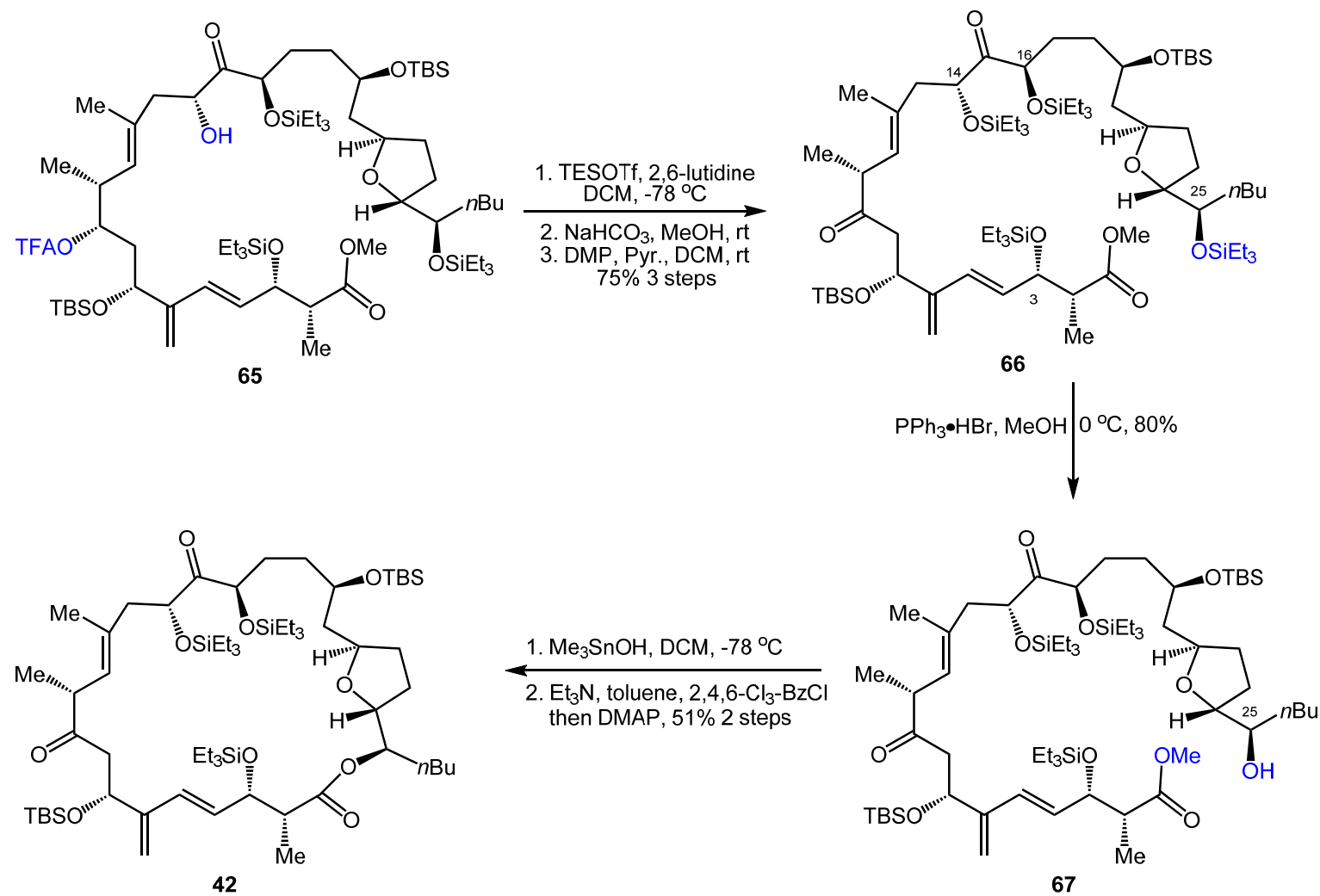
Northern Fragment Synthesis (Final Generation)



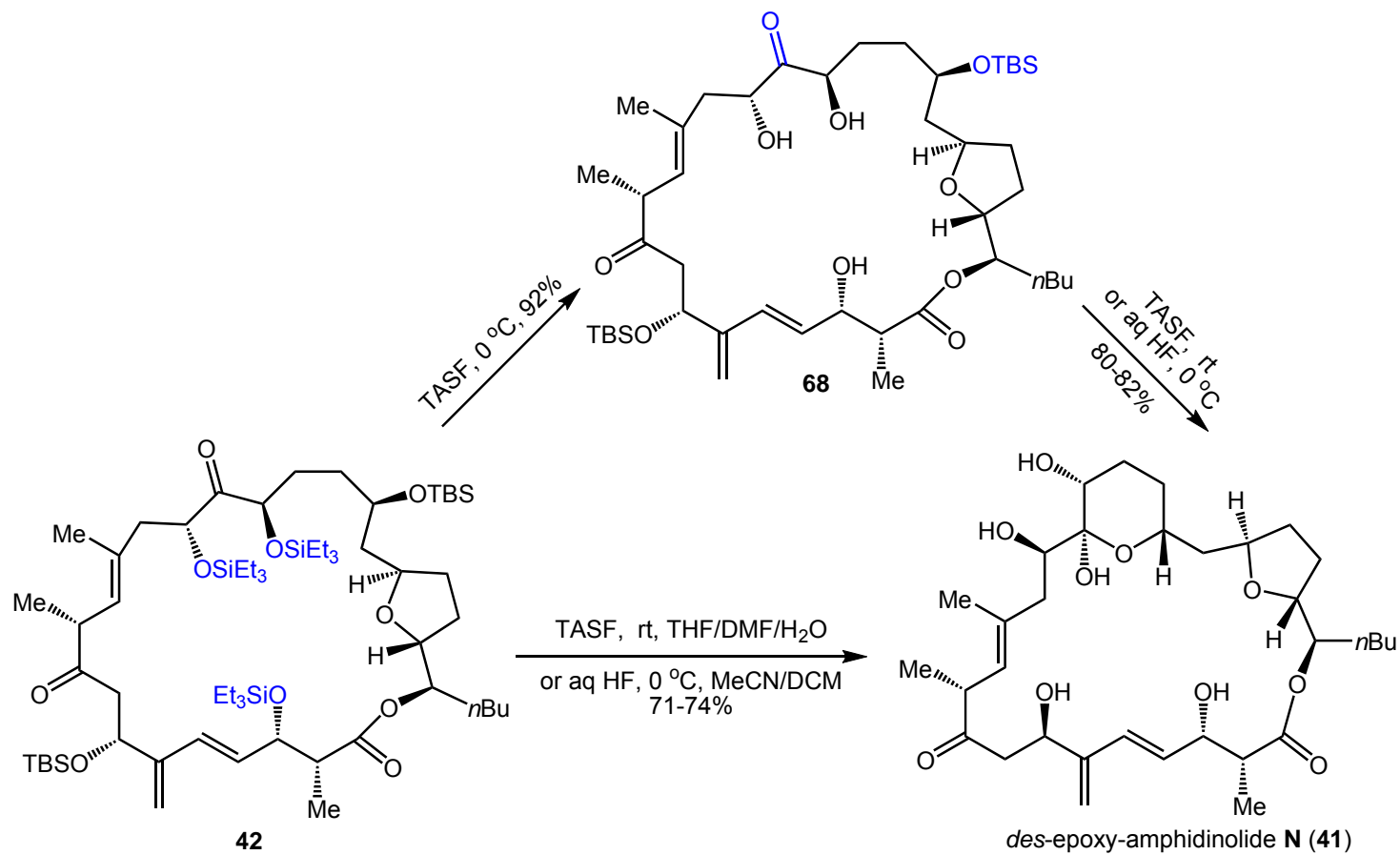
Completion of *des*-Epoxy-Amphidinolide N (41)



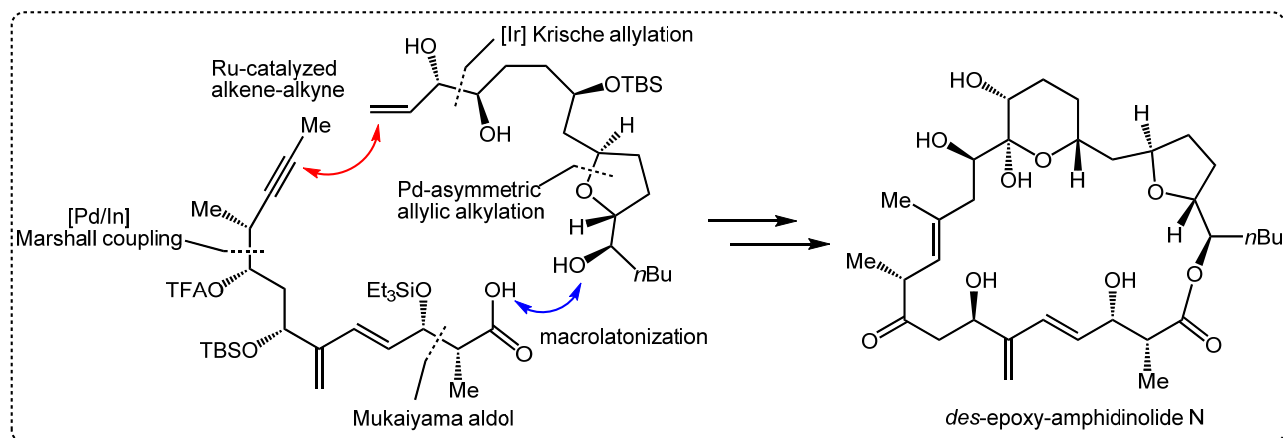
Completion of *des*-Epoxy-Amphidinolide N (41)



Completion of *des*-Epoxy-Amphidinolide N (41)



Summary



- 0.35% overall yields, 22 longest linear and 33 total steps
- Ru-catalyzed alkene-alkyne; Krische allylation; Pd-asymmetric allylic alkylation; Mukaiyama aldol; Marshall coupling; Ru-catalyzed alkene-alkyne; Keck allylation.

The First Paragraph

Macrolides provide a remarkable source for drug development due to their marvelous structural diversity and biological activity. For example, everolimus, an anti-rejection drug that is listed as one of the *Top 100 Brand Name Drugs by Retail Sales in 2016*, is essentially a rapamycin derivative. Therefore, syntheses and biological assessments of macrolides and their analogues have been enthusiastically pursued.

The amphidinolide family of natural products, isolated from the symbiotic dinoflagellates of the genus *Amphidinium* in Okinawa, is a unique class of cytotoxic macrolides. Over 40 members have been disclosed by Kobayashi, among which amphidinolide N (**1**) exhibits the most potent cytotoxicity against murine lymphoma **L1210** and human epidermoid carcinoma KB cell lines,

The First Paragraph

with IC₅₀ values of 80 and 90 pM, respectively.

The Last Paragraph

In conclusion, *des*-epoxy-amphidinolide **N** (**3**) was accomplished in 22 longest linear and 33 total steps. The synthesis took advantage of a convergent design that efficiently joined two fragments with similar levels of structural complexity using a Ru-catalyzed alkene-alkyne coupling and a macrolactonization. Three generations of synthetic endeavors were reported. The first generation validated the key Ru AA coupling stitching strategy and realized a challenging chemoselective allylic epoxidation of a complex macrocycle, but left installation of the α,α' -dihydroxy ketone moiety and scalable preparation of the southern fragment as unanswered questions. The second generation addressed the scalability of the southern fragment synthesis and significantly improved the Ru AA

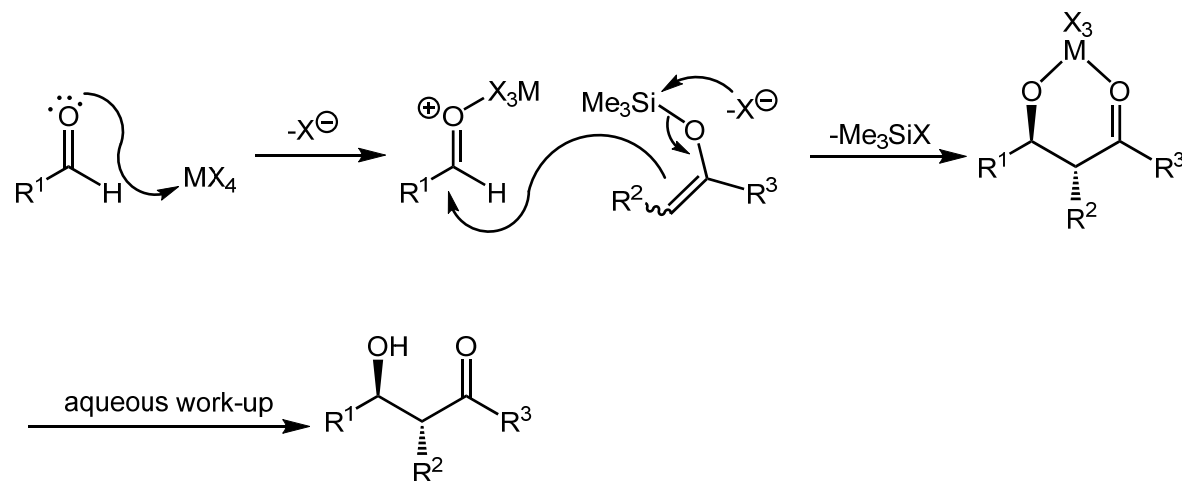
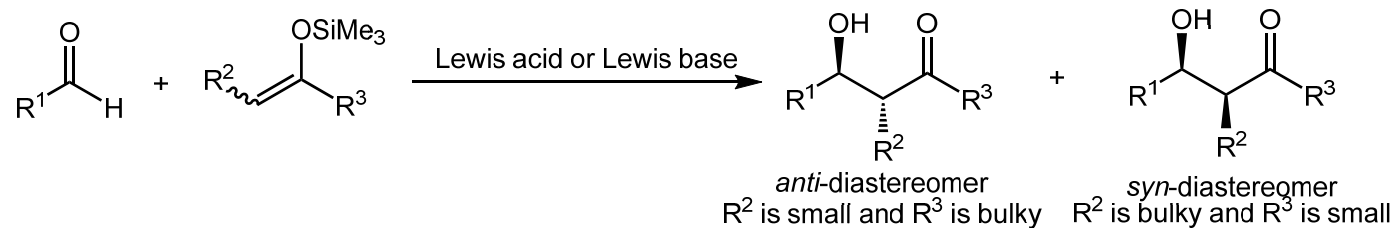
The Last Paragraph

coupling efficiency, but revealed that the thioether was incompatible with the Rubottom oxidation alongside the deprotection troubles. Evolving from these two generations of synthetic efforts, the final generation not only logically designed the whole protecting group strategy but also successfully installed the C14-OH via a carefully tuned Rubottom oxidation, allowing us to realize the synthesis of *des*-epoxy-amphidinolide **N**. Several remarkable asymmetric transition-metal-catalyzed reactions were deployed, including Mukaiyama aldol (Sn), Marshall coupling (Pd–In), Pd-AAA (Pd), and Krische allylation (Ir). Structural elucidation of the THP ring of *des*-epoxy-amphidinolide **N** (**41**) not only verified our assignments but also led us to disclose the hydrogen-bonding network in

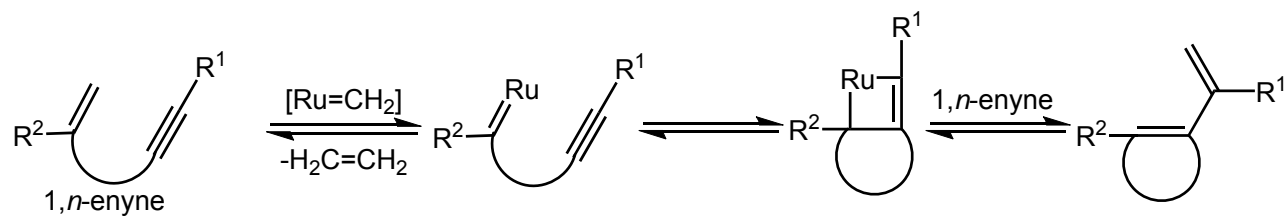
The Last Paragraph

amphidinolide **N** (1).

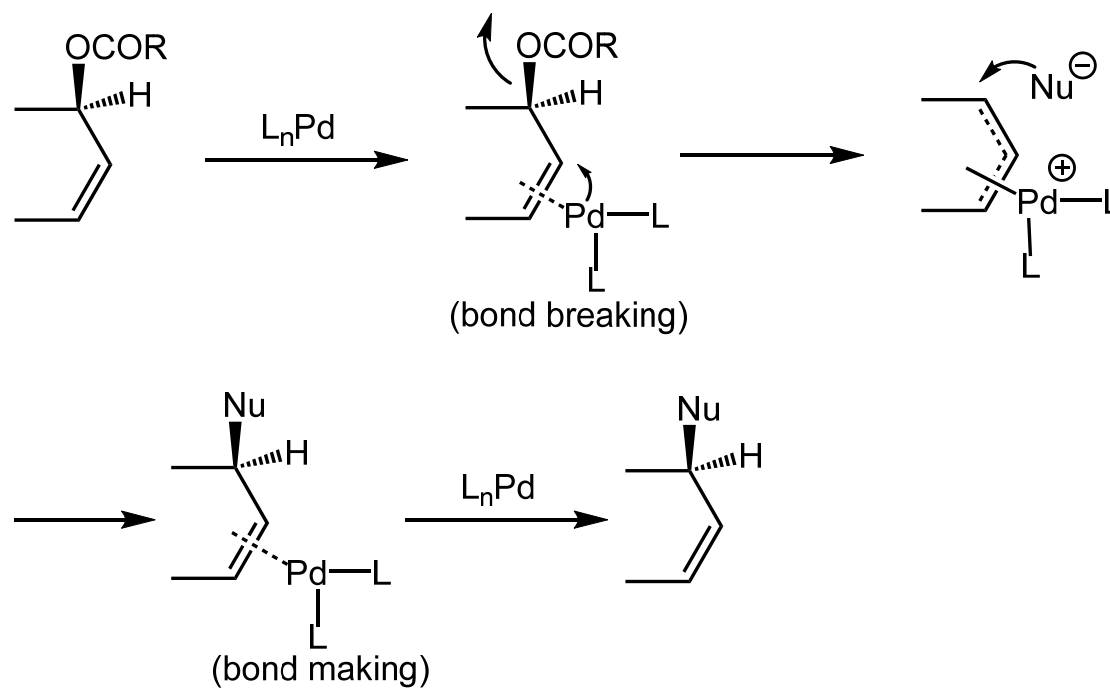
Mukaiyama Aldol Reaction



Enyne Metathesis

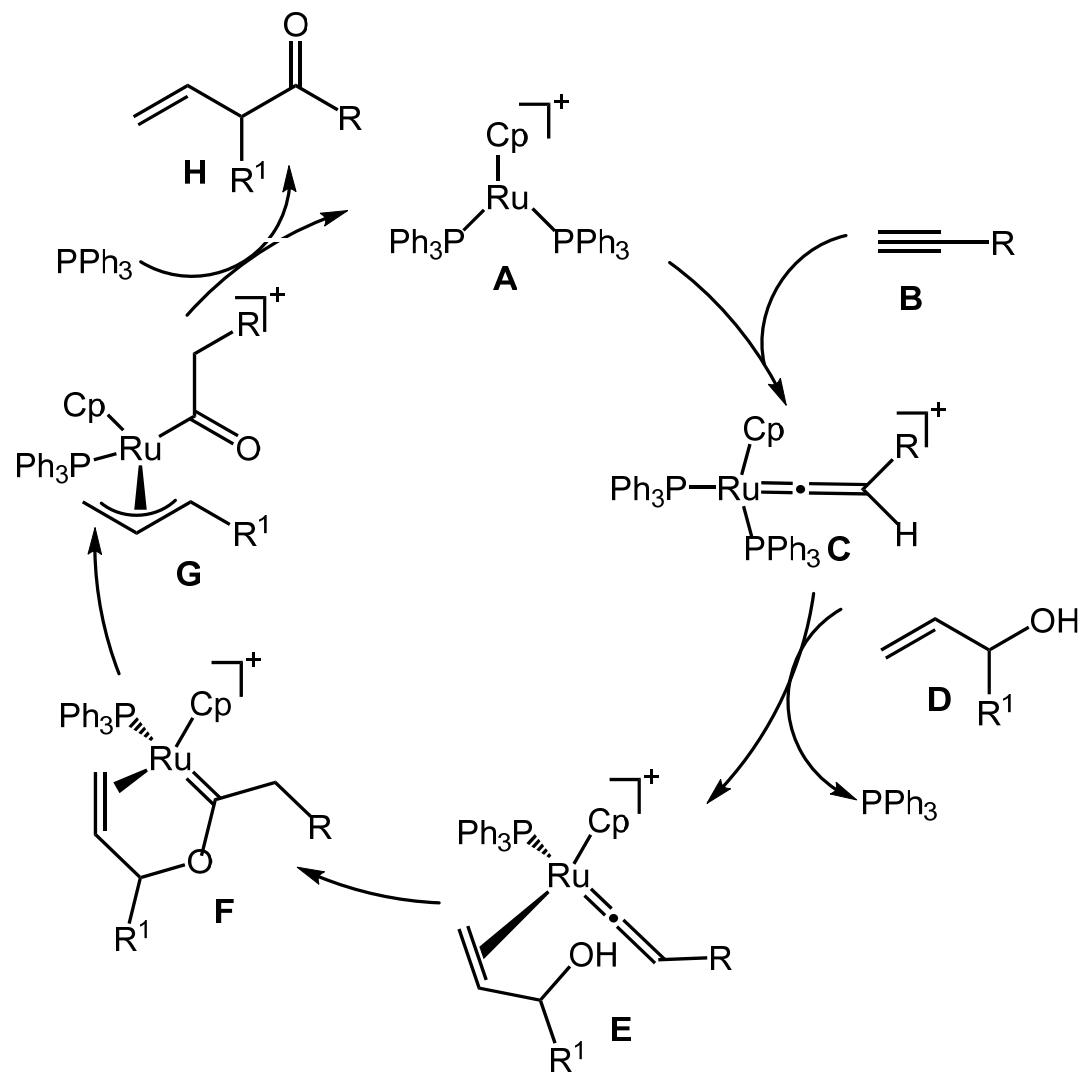


Pd-catalyzed Asymmetric Allylic Alkylation



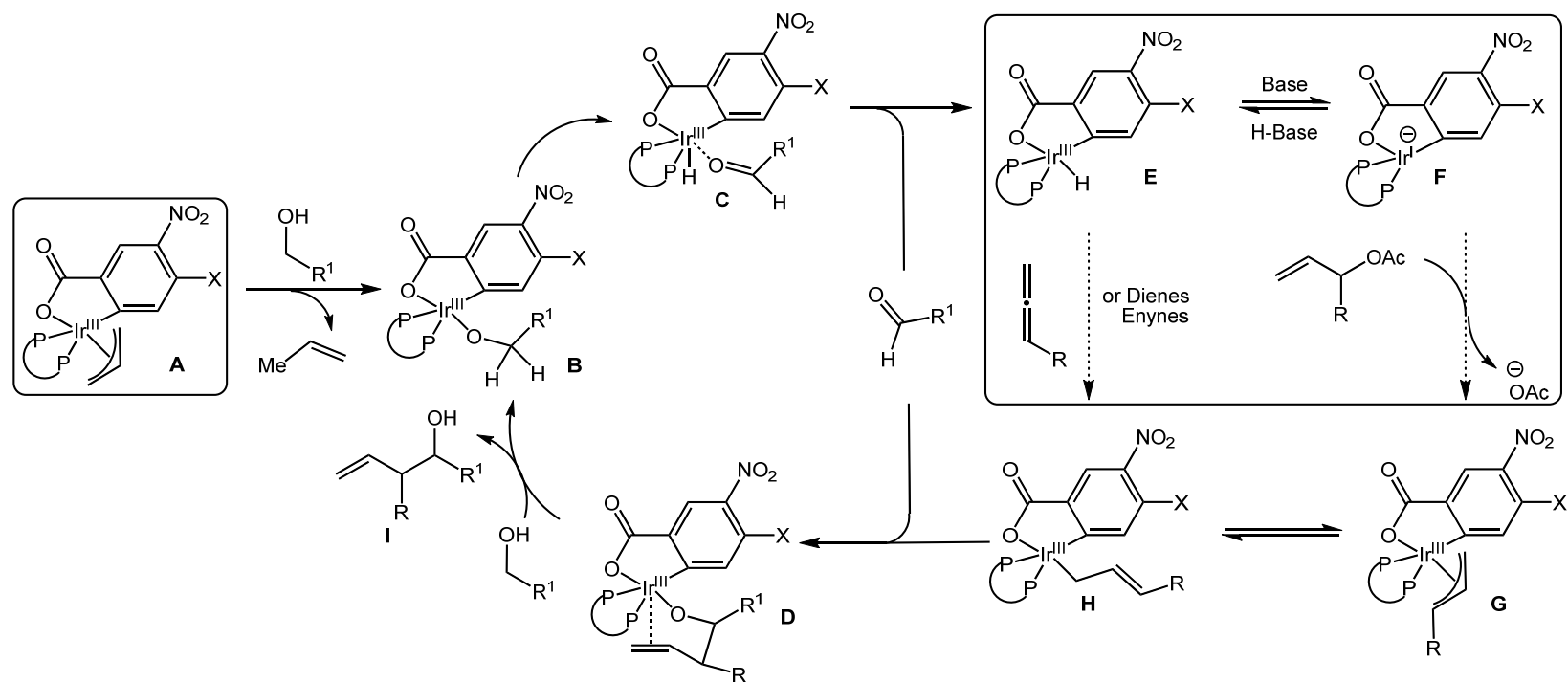
Trost, B. M. *Org. Process Res. Dev.* **2012**, *16*, 185.

Ru AA Coupling



Trost, B. M.; *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 6630.

Krische Allylation



Krische, M. J.; *et al.* *J. Am. Chem. Soc.* **2016**, *138*, 5467.

Keck Asymmetric Allylation

