Total Synthesis of Spirastrellolide F

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Spirastrella coccinea

Current literature
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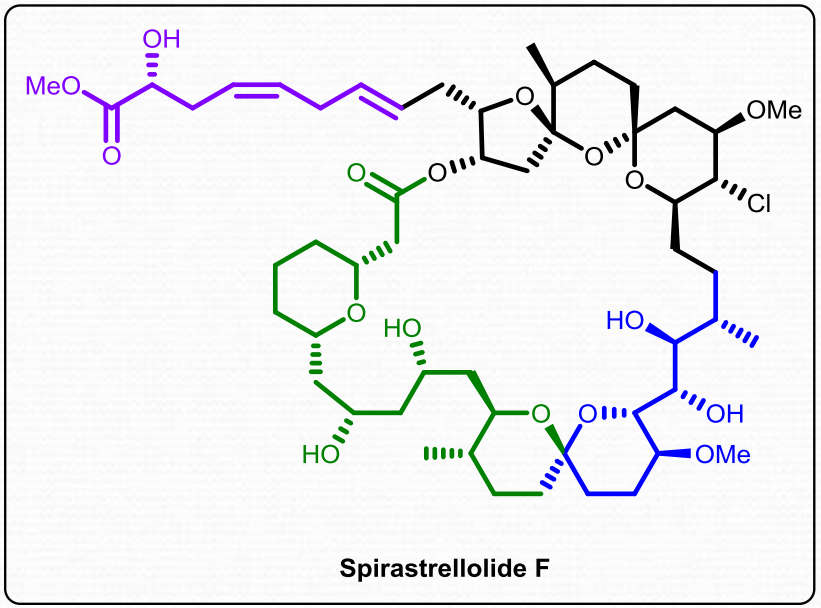
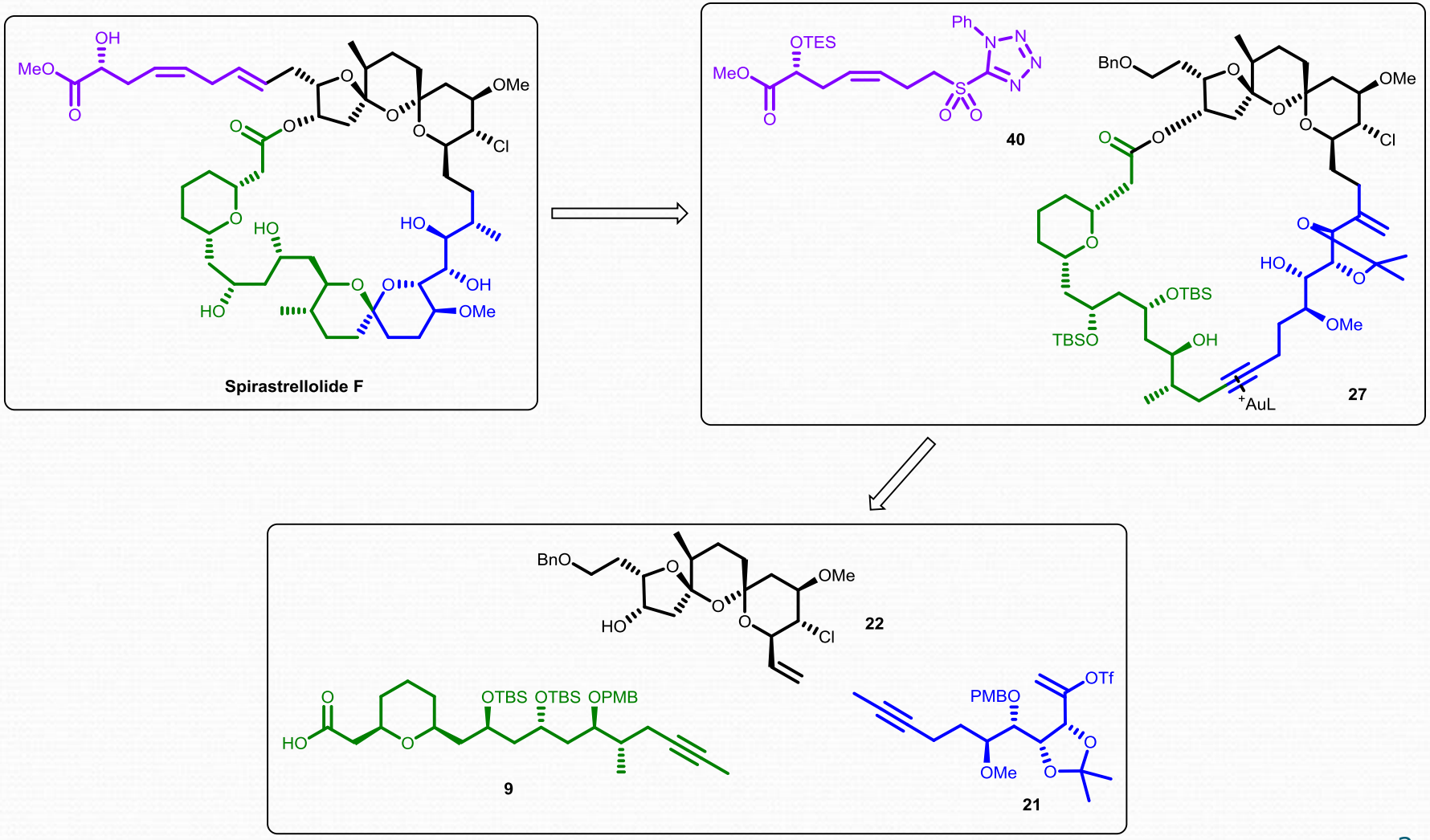
Introduction

- Spirastrellolide F was isolated by Andersen and co-workers from the Caribbean sponge *Spirastrella coccinea* in 2007.
- Selective inhibitors of the serine/threonine protein phosphatase PP2 A (IC_{50} = 1 nM)

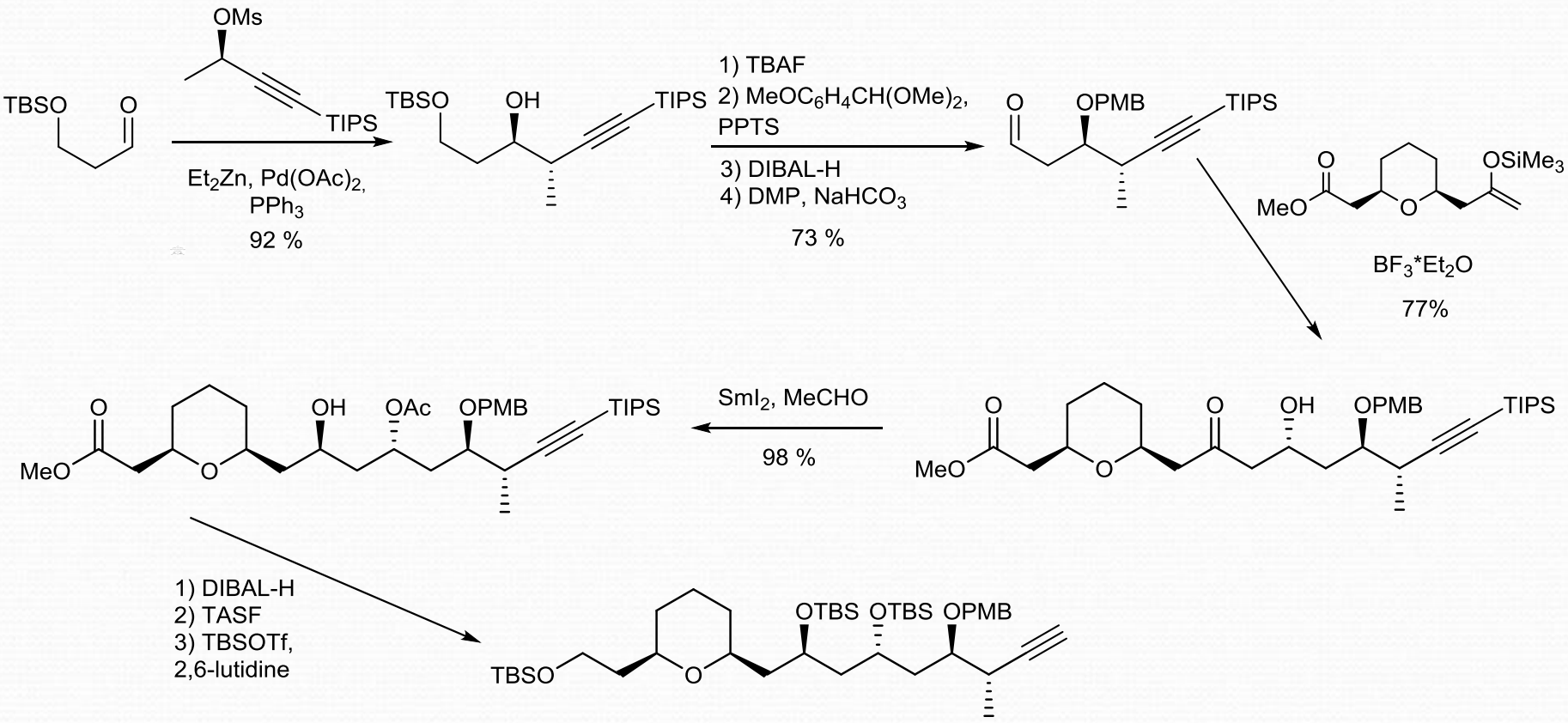


Spirastrellolide F

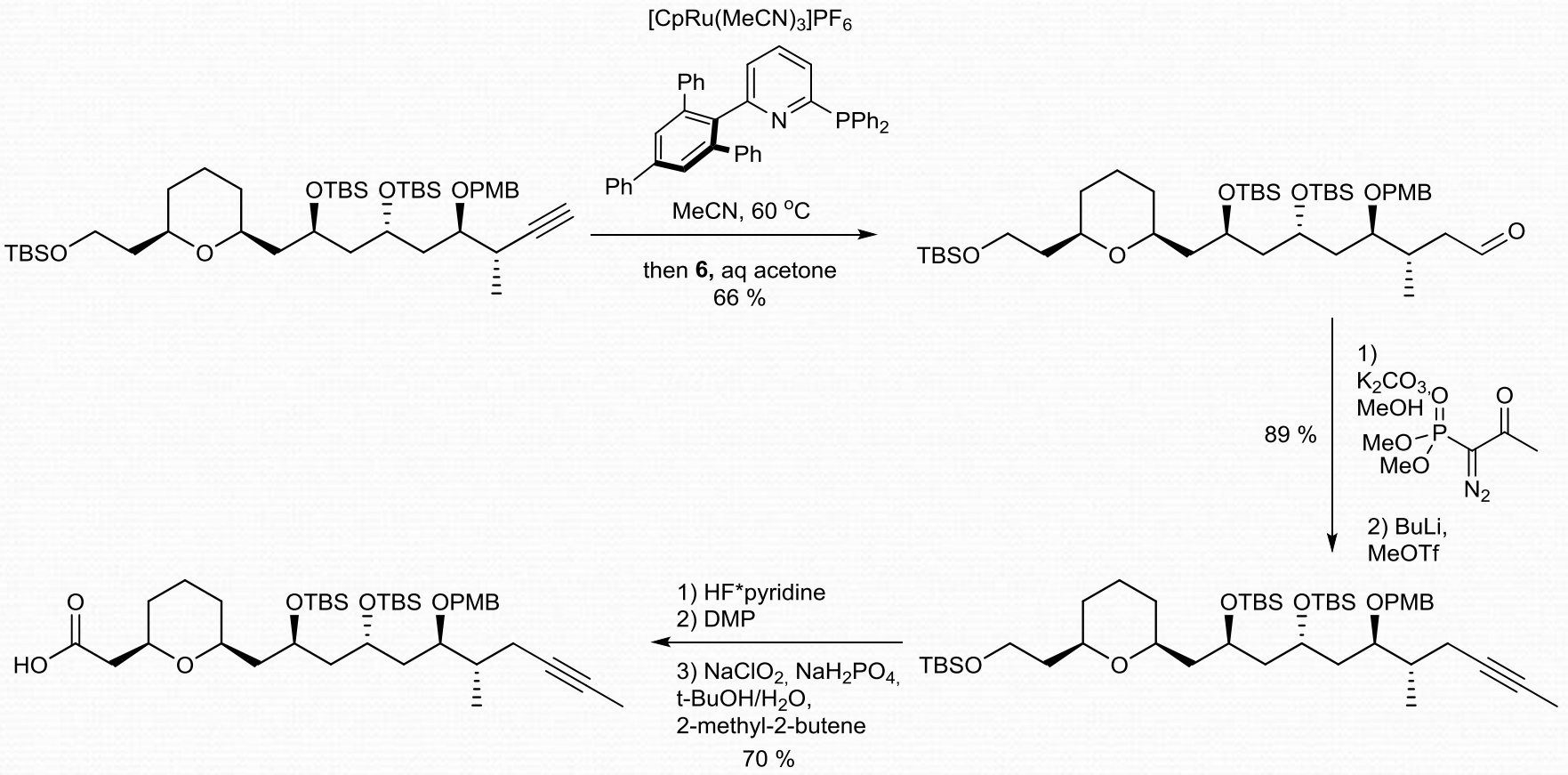
Retrosynthetic Analysis of Spirastrellolide F



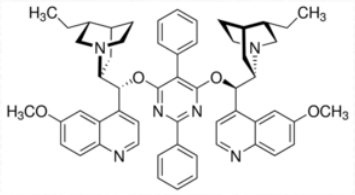
Synthesis of Building Block 9

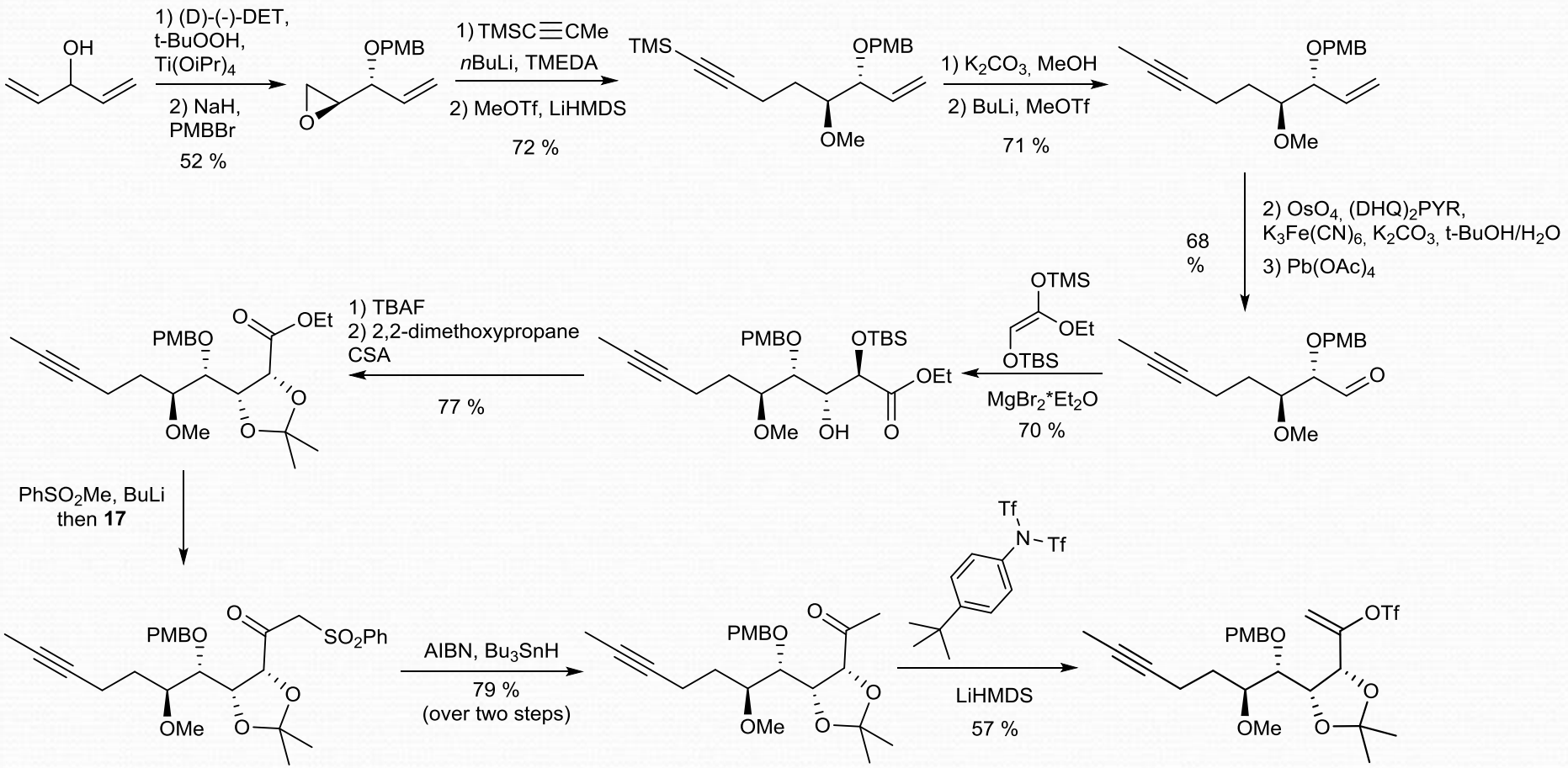


Synthesis of Building Block 9

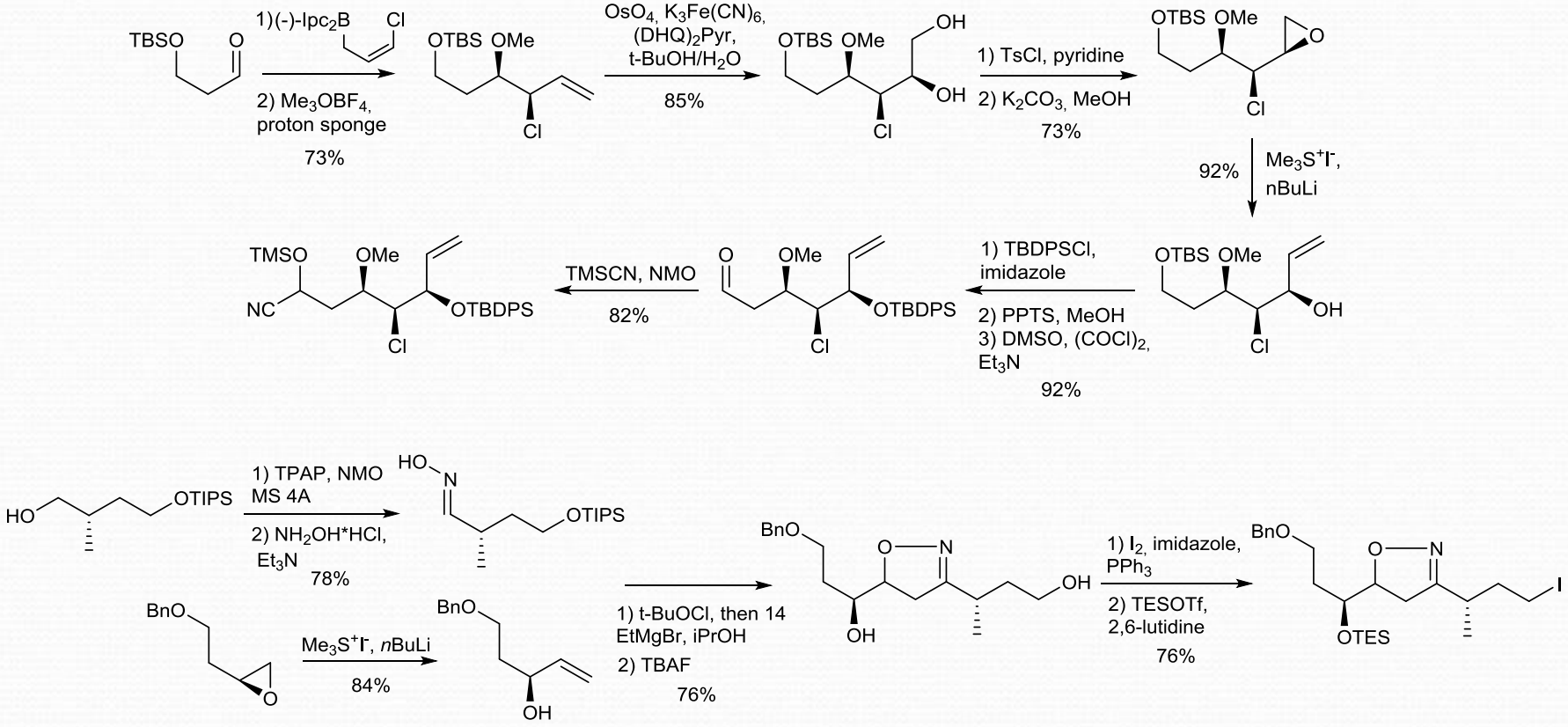


Synthesis of Building Block 21

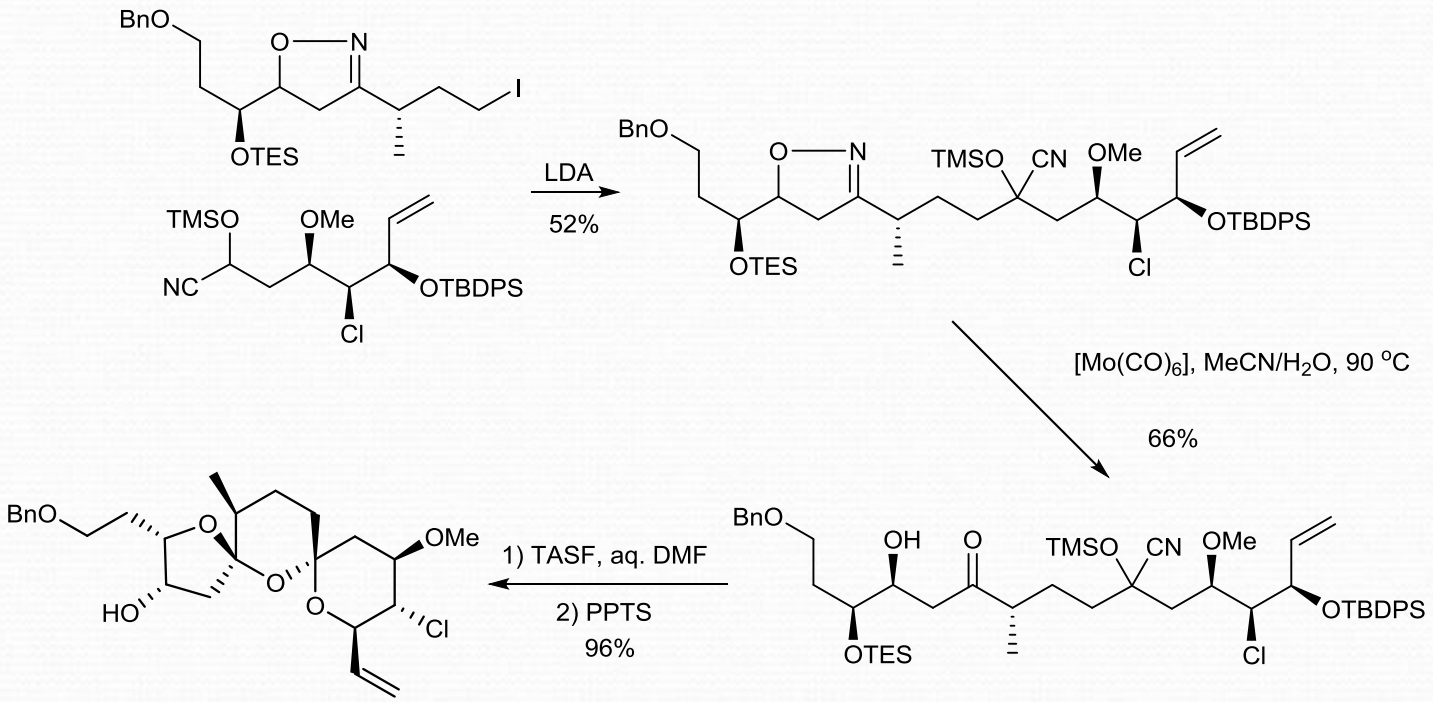




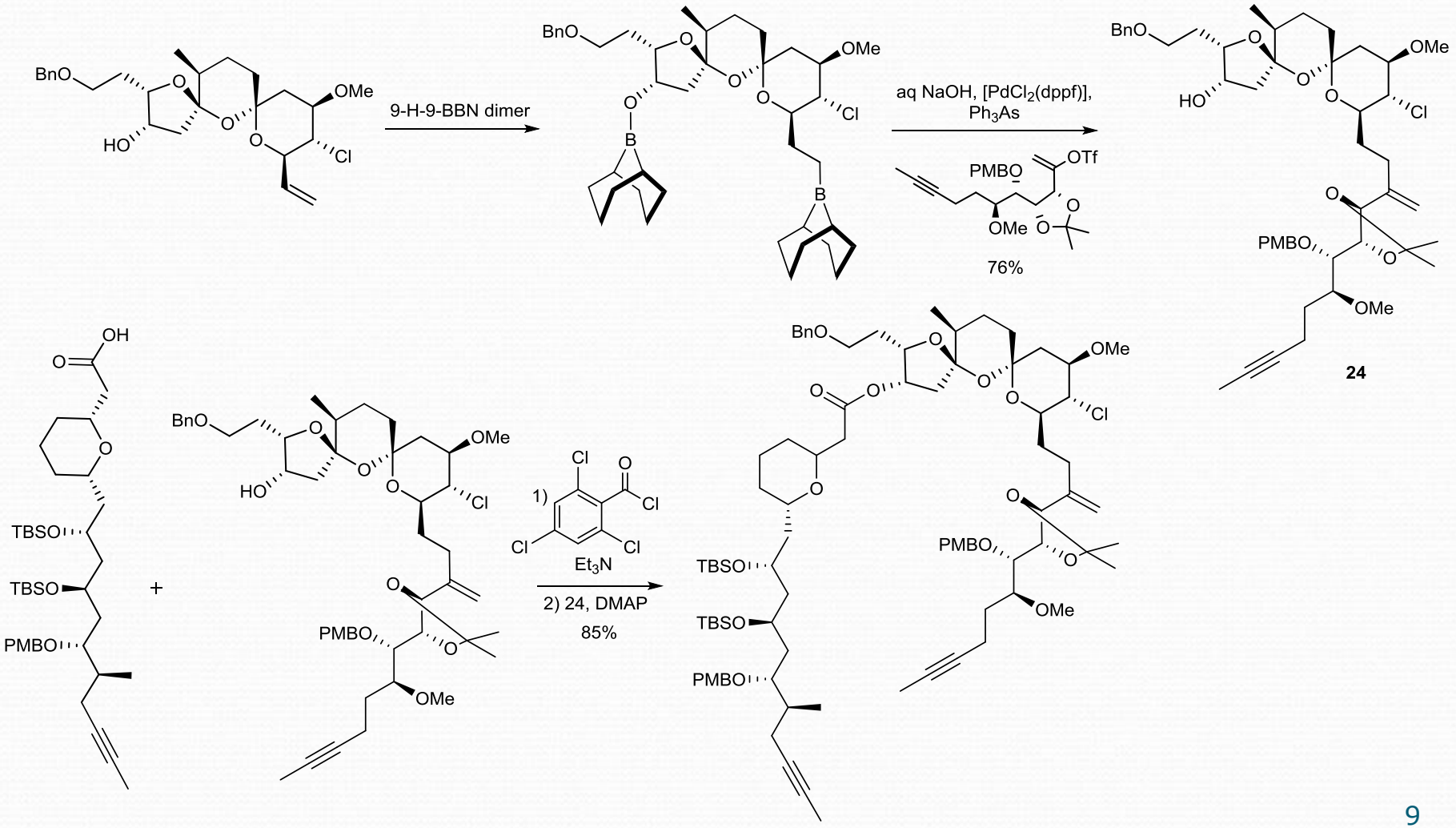
Synthesis of Precursors for Building Block 22



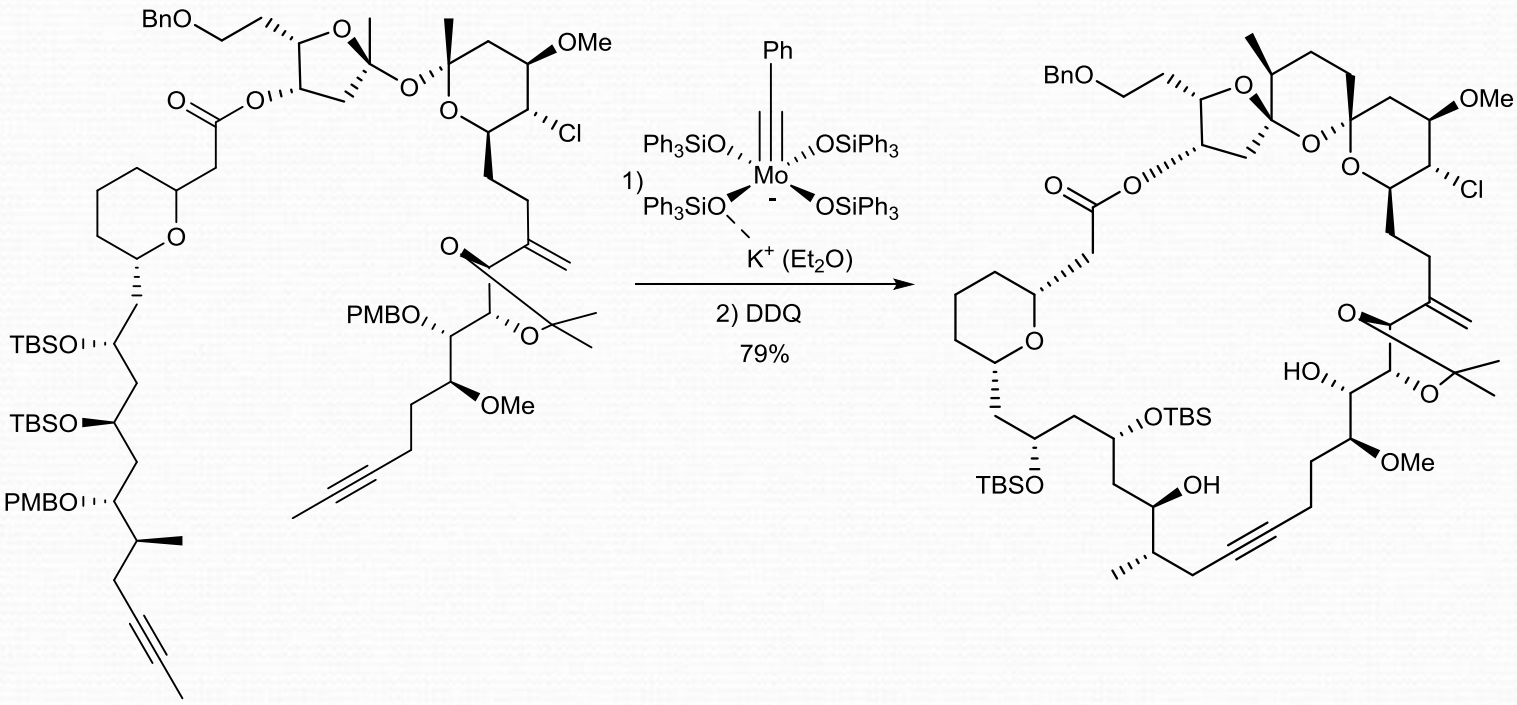
Synthesis of Building Block 22



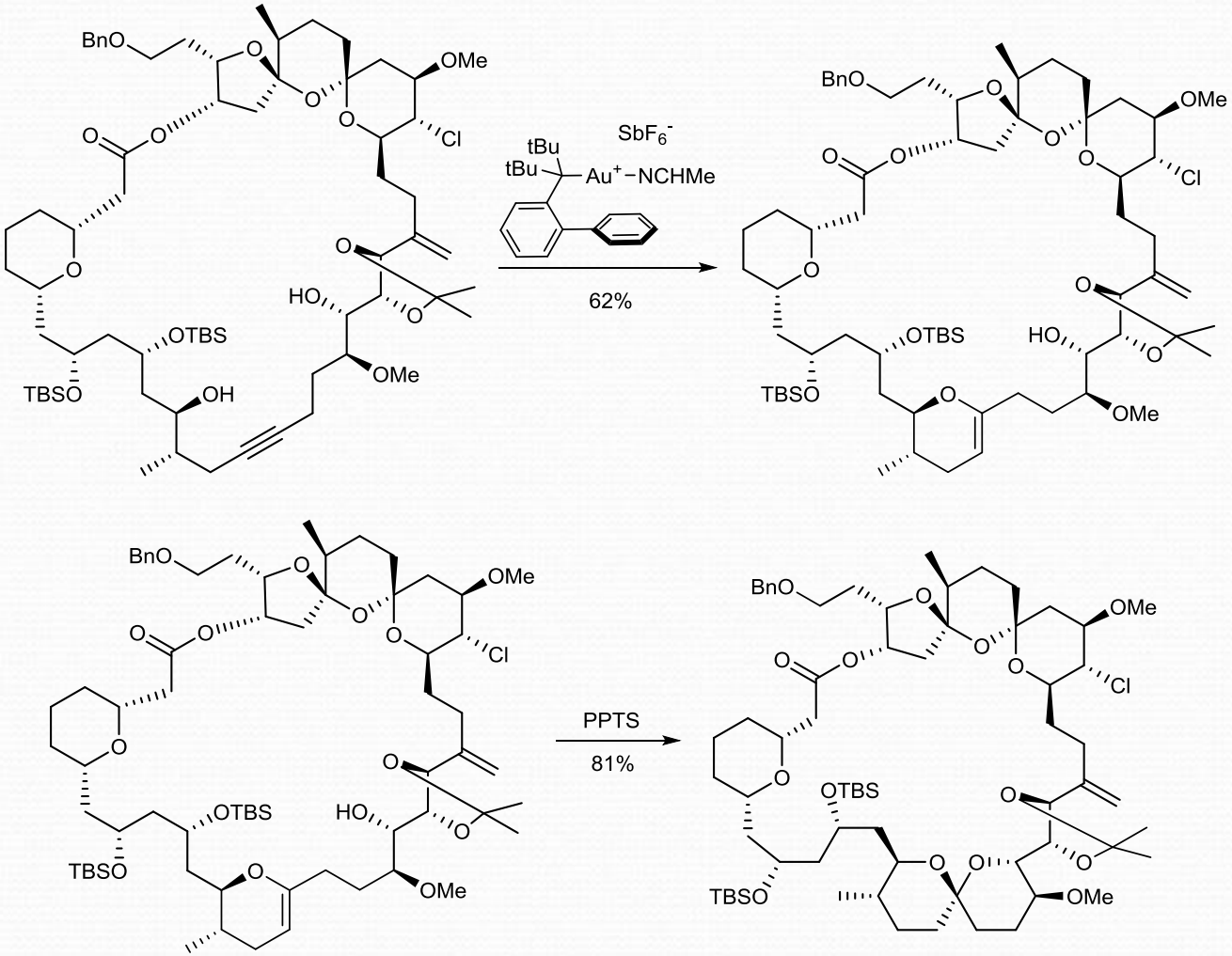
Synthesis of Building Block 31



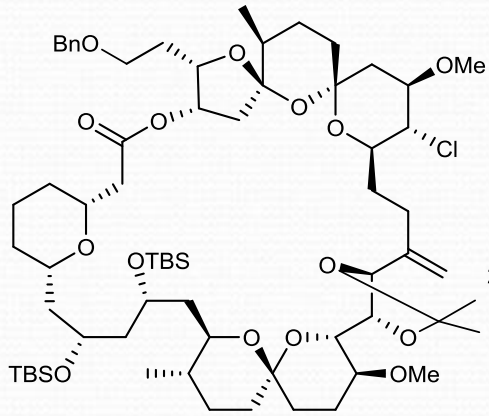
Synthesis of Building Block 31



Synthesis of Building Block 31



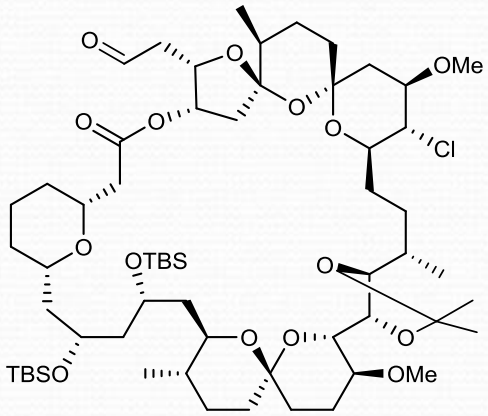
Completion of the Total Synthesis

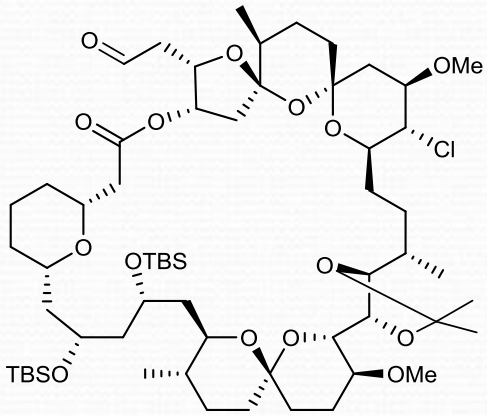


1) $Pd(OH)_2$, H_2, EtOAc, 1 atm

2) DMP, $NaHCO_3$

67%





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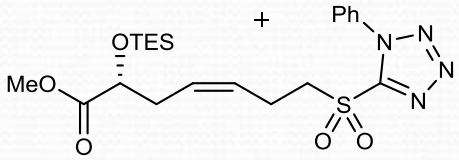
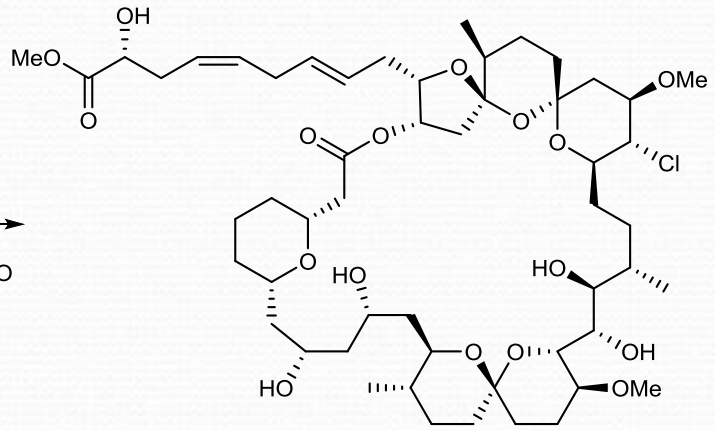


1) KHMDS, THF

2) PPTS, $MeOH/Et_2O/H_2O$

42%



Spirastrellolide F

Conclusions

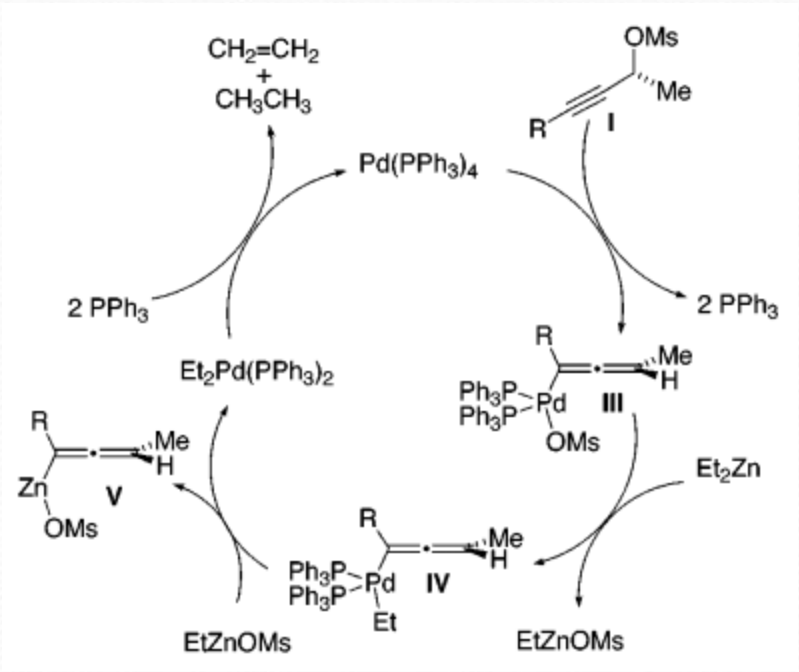
Second-generation total synthesis of the complex antimitotic macrolide Spirastrellolide F methyl ester.

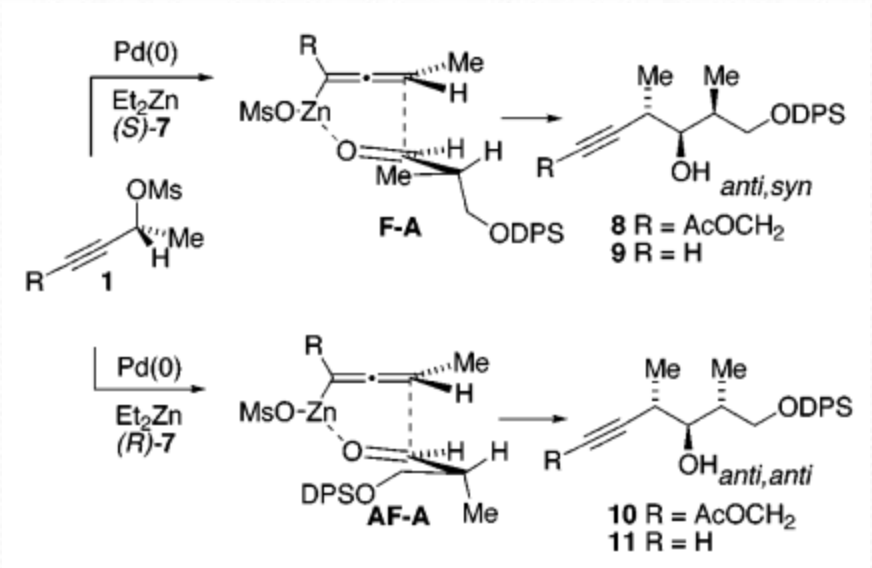
Key-steps:

- Ring-closing alkyne metathesis.
- Formation of the «southern» acetal domain by carbophilic activation of the π-bond by gold complex.
- Formation of the «northern hemisphere» by Yamaguchi esterification and alkyl-Suzuki cross-coupling reaction.
- Julia-Kocienski olefination between macrolide ring and side chain.

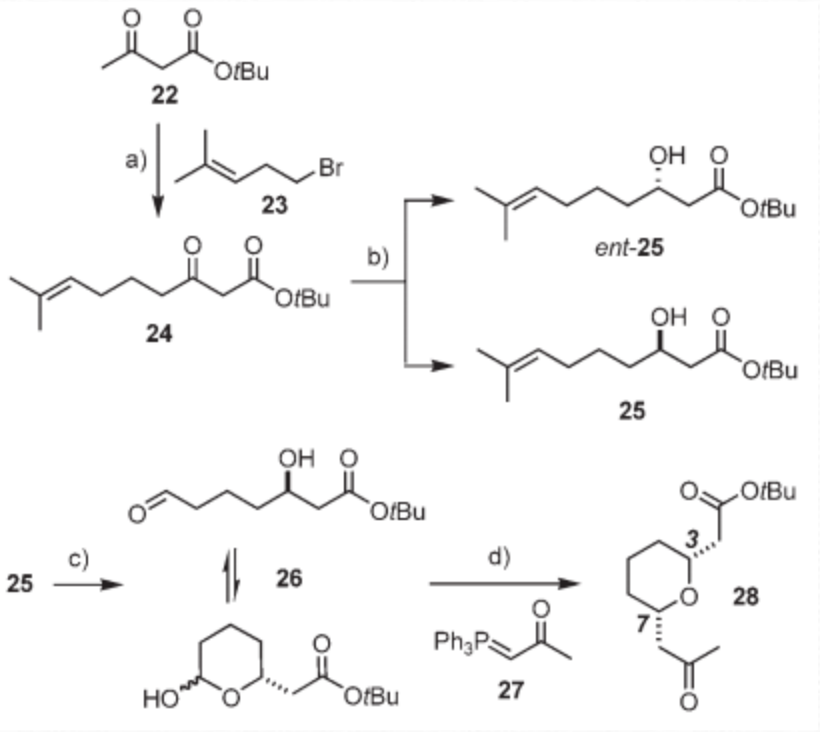
Thank you for your attention!

Marshall Propargylation



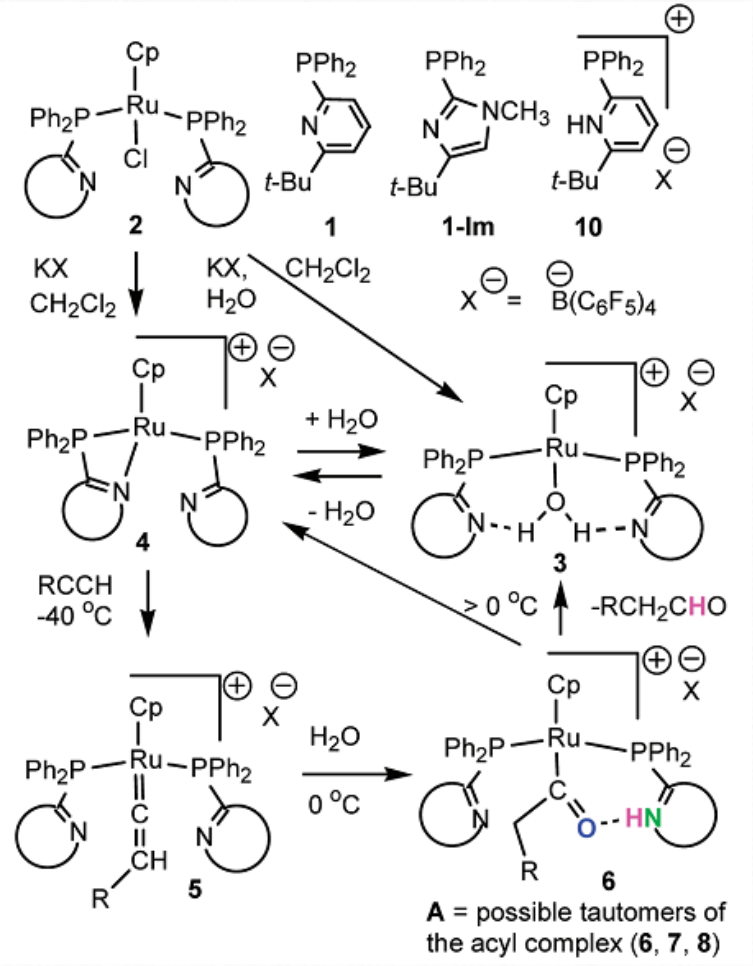


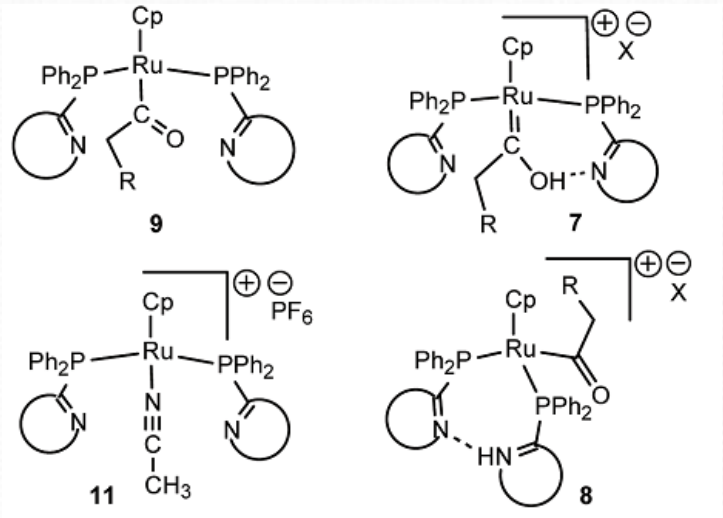
Synthesis of Tetrahydropyran



Scheme 6. Preparation of segment **D**. Reagents and conditions: a) NaH, *n*BuLi, then bromide **23**, THF/HMPA (81%); b) $[RuCl_2$-(binap)$]_2$-NEt_3 (1 mol%), HCl (2 mol%), H_2 (5 bar), MeOH, 40°C (95%; 98% *ee*); c) O_3, MeOH, then Me_2S, −78°C→RT; d) 1. ylide **27**, toluene, reflux; 2. CSA cat., CH_2Cl_2 (78%; 3 steps; d.r. = 8.5:1). binap = (1,1′-binaphthalene)-2,2′-diylbis(diphenylphosphine), HMPA = hexamethyl phosphoramide.

Ruthenium-Catalyzed Hydration





Sharpless Epoxidation