Literature Report I

Total Synthesis of (-)-Nahuoic Acid C_i (B_{ii})

Reporter: Xin-Wei Wang
Checker: Shu-Bo Hu
Date: 2017-11-20

Liu, Q.; Deng, Y.; Smith, A. B. III
J. Am. Chem. Soc. **2017**, *139*, 13668-13671.

CV of Professor Smith, A. B. III

Background:

- **1962-1966** B.S. & M.S. in Bucknell University;
- **1967-1972** Ph.D. in Rockefeller University;
- **1972-1973** RA in Rockefeller University;
- **1973-2017** University of Pennsylvania;
- **1998-2017** Editor-in-Chief of *Organic Letters*.

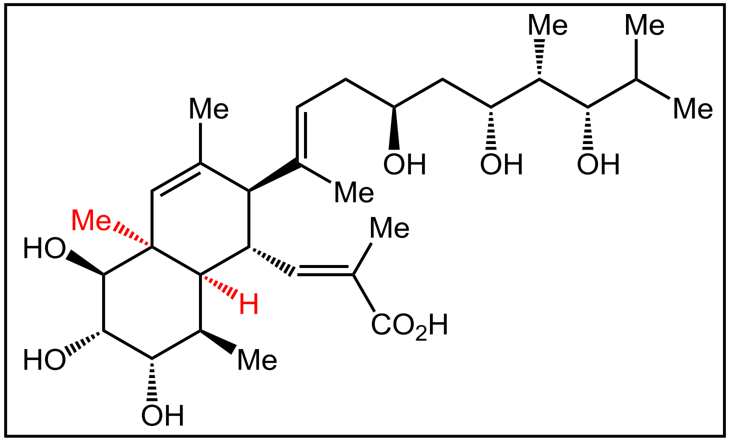
Smith, A. B. III

Research:

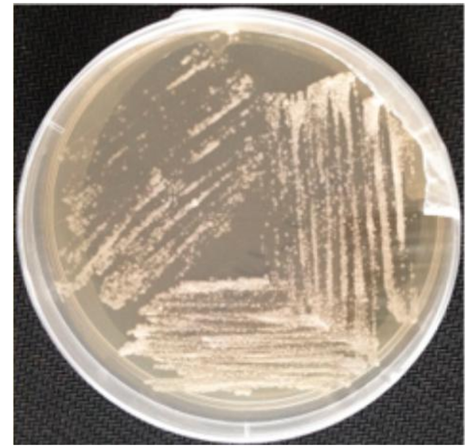
- Natural Product Synthesis;
- Bioorganic Chemistry;
- Materials Science.

Contents

Introduction



(-)-Nahuoic Acid C_i (B_{ii})

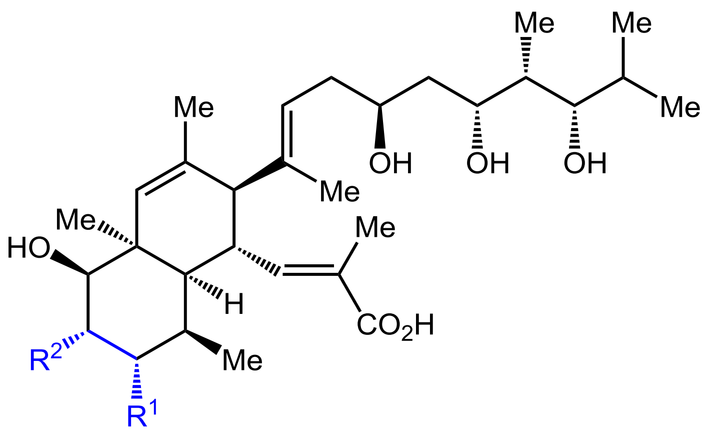


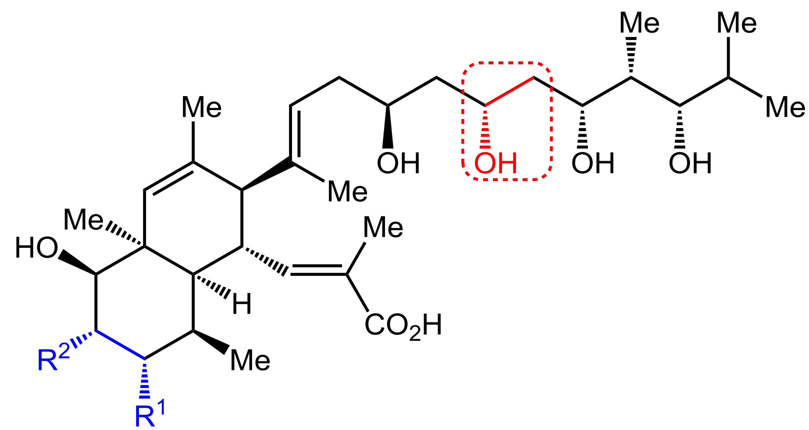
SCSGAA 0027

- It was isolated from Streptomyces sp. in 2016;
- It displays selective (*S*)-adenosylmethionine (SAM)-competitive inhibitor activity against the histone lysine methyltransferase SETD8 enzyme;
- It features 12 stereocenters and *cis*-decalin motifs in conjunction with polyol side chains.

Williams, D. E.; Izard, F.; Arnould, S.; Andersen, R. J. *J. Org. Chem.* **2016**, *81,* 1324-1332.
Nong, X.-H.; Zhang, X.-Y.; Xu, X.-Y.; Wang, J.; Qi, S.-H. *J. Nat. Prod*. **2016**, *79*, 141-148.

Introduction





Nahuoic Acid

A: R_1 = OH, R_2 = H (**1**)
B_i: R_1 = H, R_2 = OH (**2**)
C_i (B_{ii}): R_1 = R_2 = OH (**3**)
C_{ii}: R_1 = R_2 = H (**4**)

D_i (E_i): R_1 = OH, R_2 = H (**5**)
E_i: R_1 = H, R_2 = OH (**6**)
D_{ii}: R_1 = R_2 = H (**7**)

Williams, D. E.; Dalisay, D. S.; Li, F.; Amphlett, J.; Andersen, R. J. *Org. Lett*. **2013**, *15*, 414-417.
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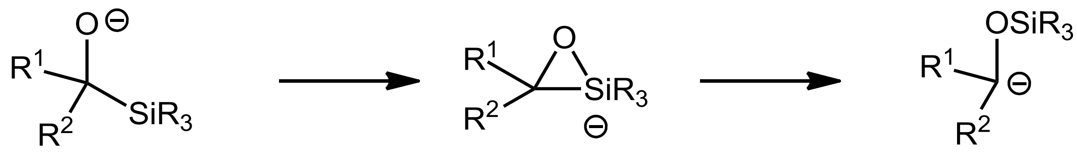
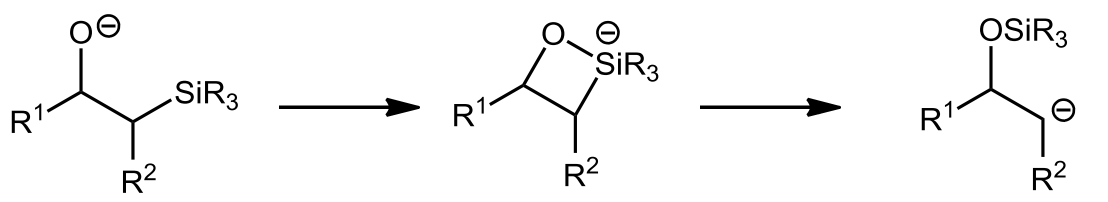
Brook Rearrangement

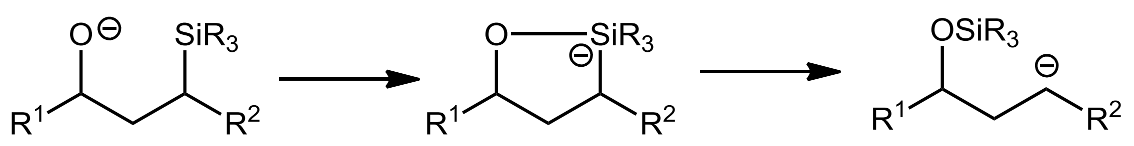
[1,2]-Brook rearrangement



[1,3]-Brook rearrangement



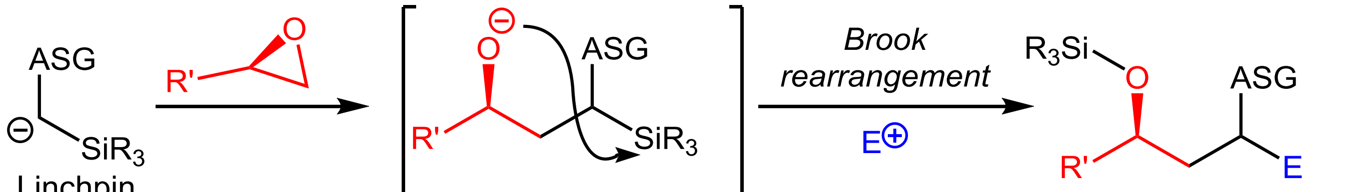
[1,4]-Brook rearrangement



驱动力：氧对硅有更强的亲和力
键能：O-Si = 460 kJ/mol；C-Si = 346 kJ/mol

Type I and II ARC Tactics

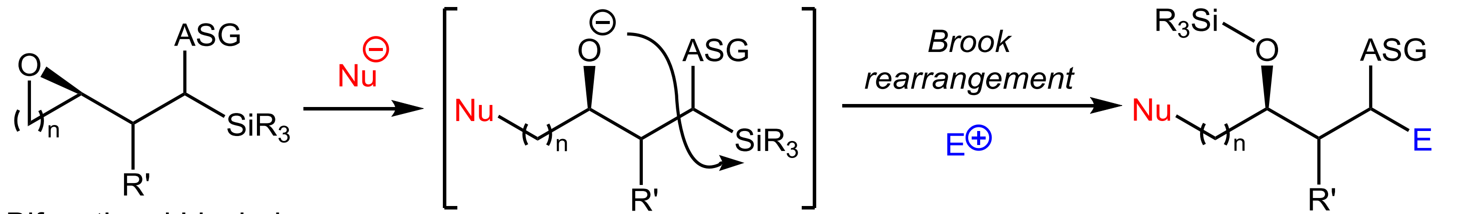
A. Type I ARC (Anion Relay Chemistry)



Linchpin

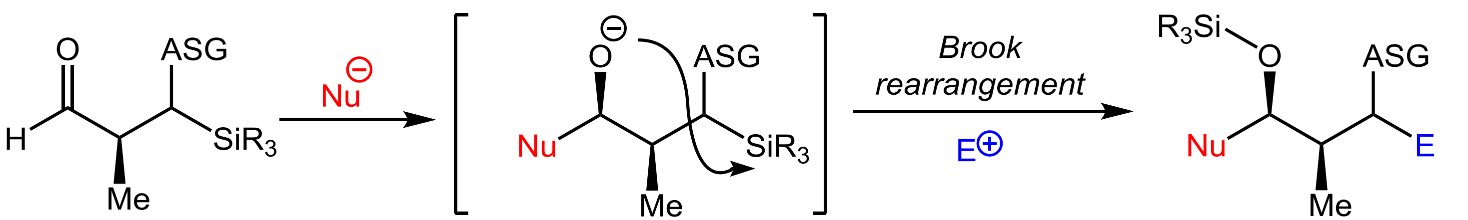
Tricomponent adduct

B. Type II ARC (Anion Relay Chemistry)



Bifunctional Linchpin
n = 0, 1

Tricomponent adduct

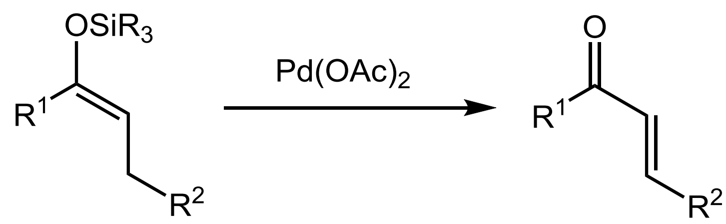


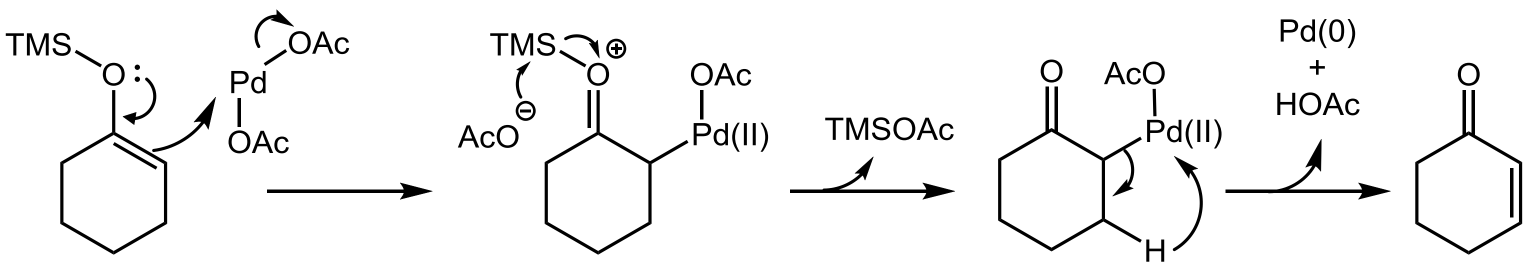
Linchpin

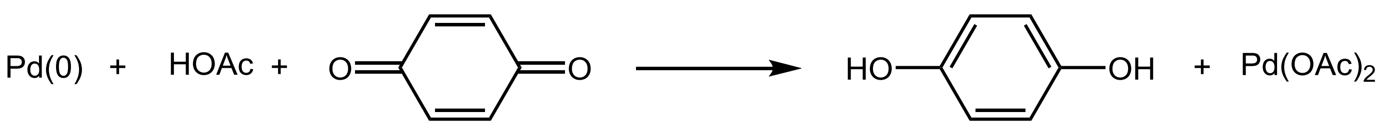
Tricomponent adduct

ASG = Anion Stabilizing Group

Saegusa–Ito oxidation

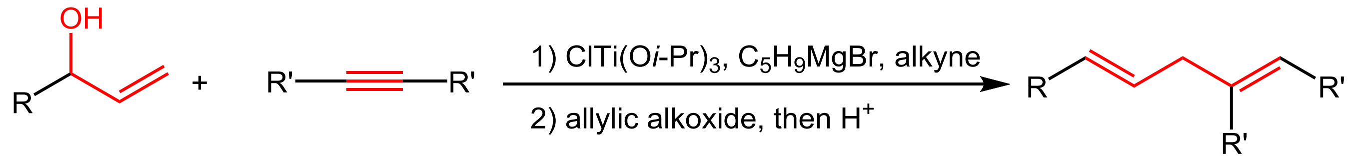


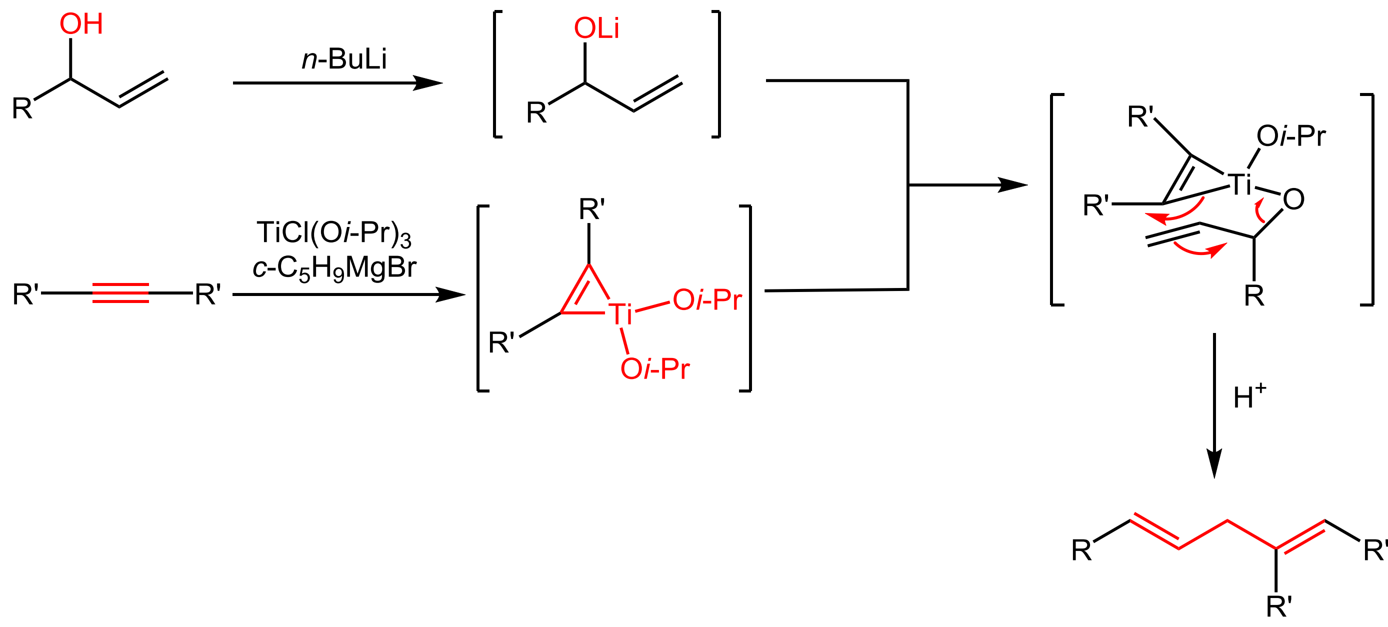




From Name Reactions by Jie Jack Li

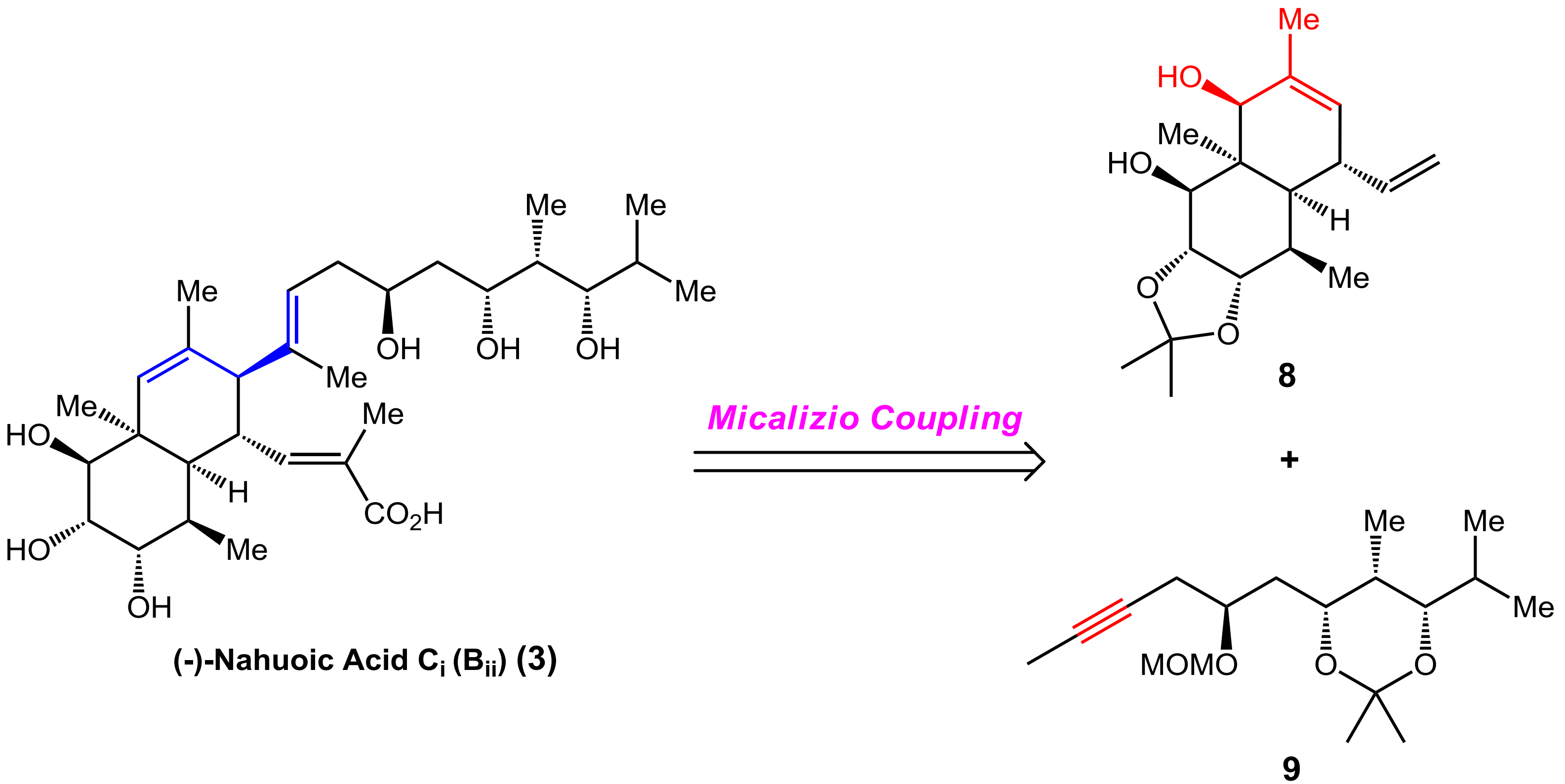
Micalizio Coupling





Kolundzic, F.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 15112-15113.

Retrosynthetic Analysis



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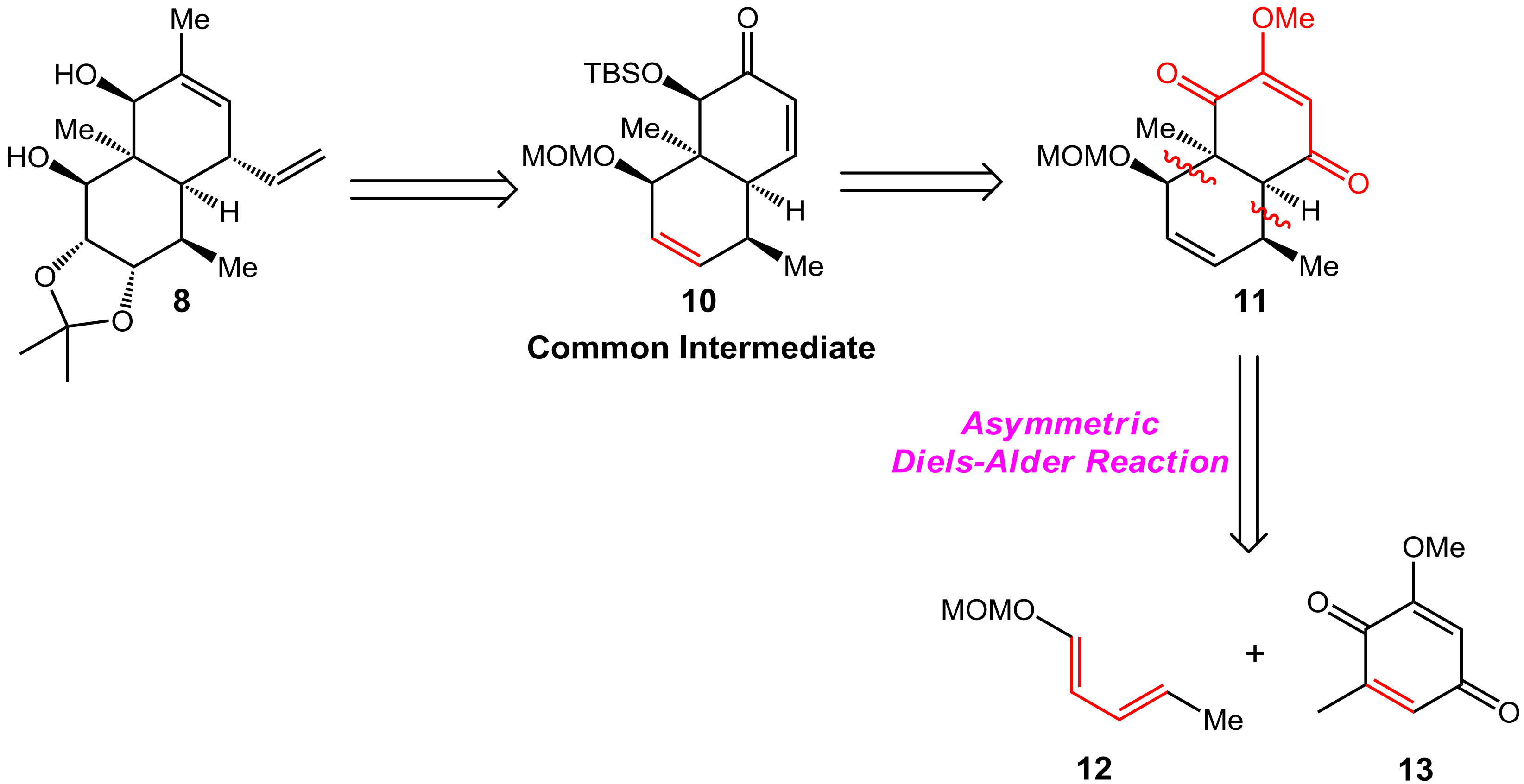
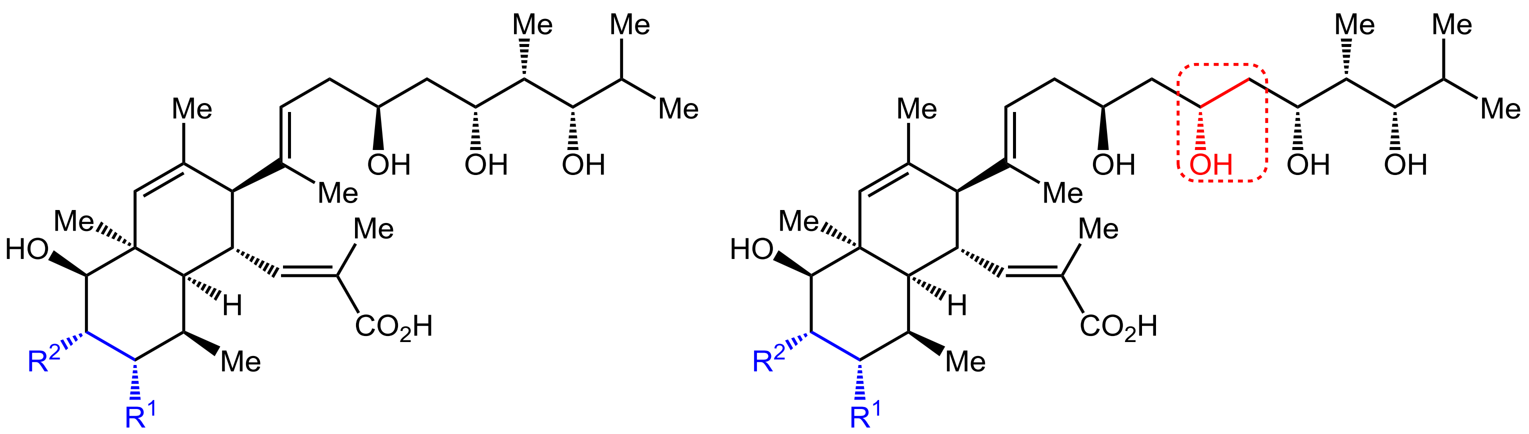


Structures of nahuoic acids



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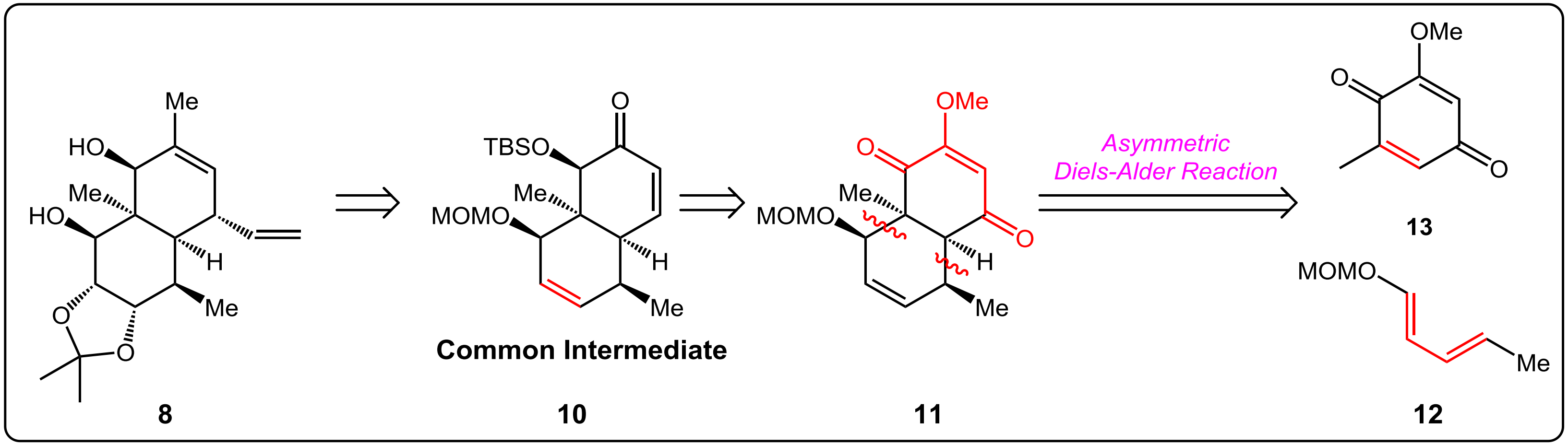
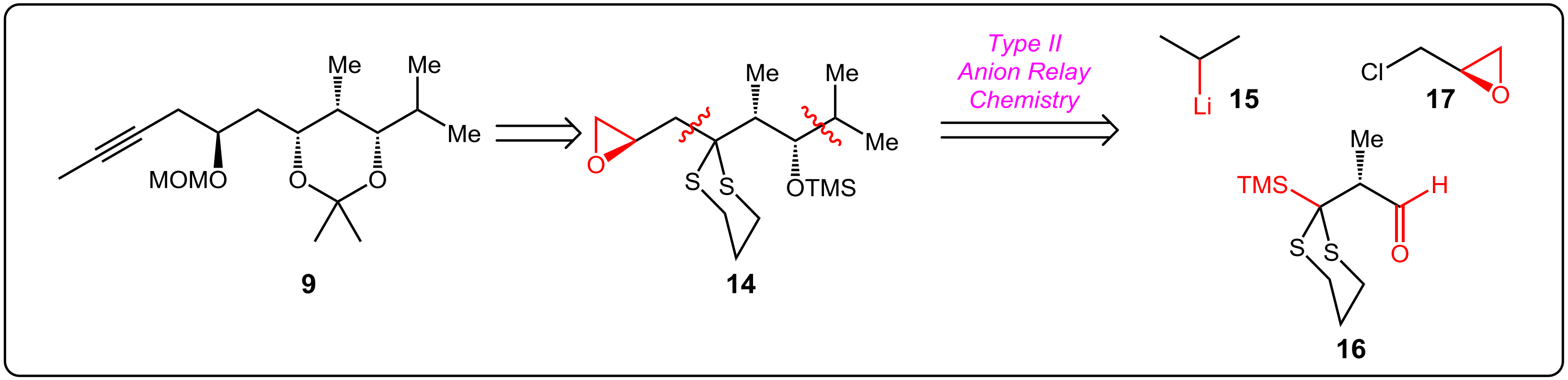
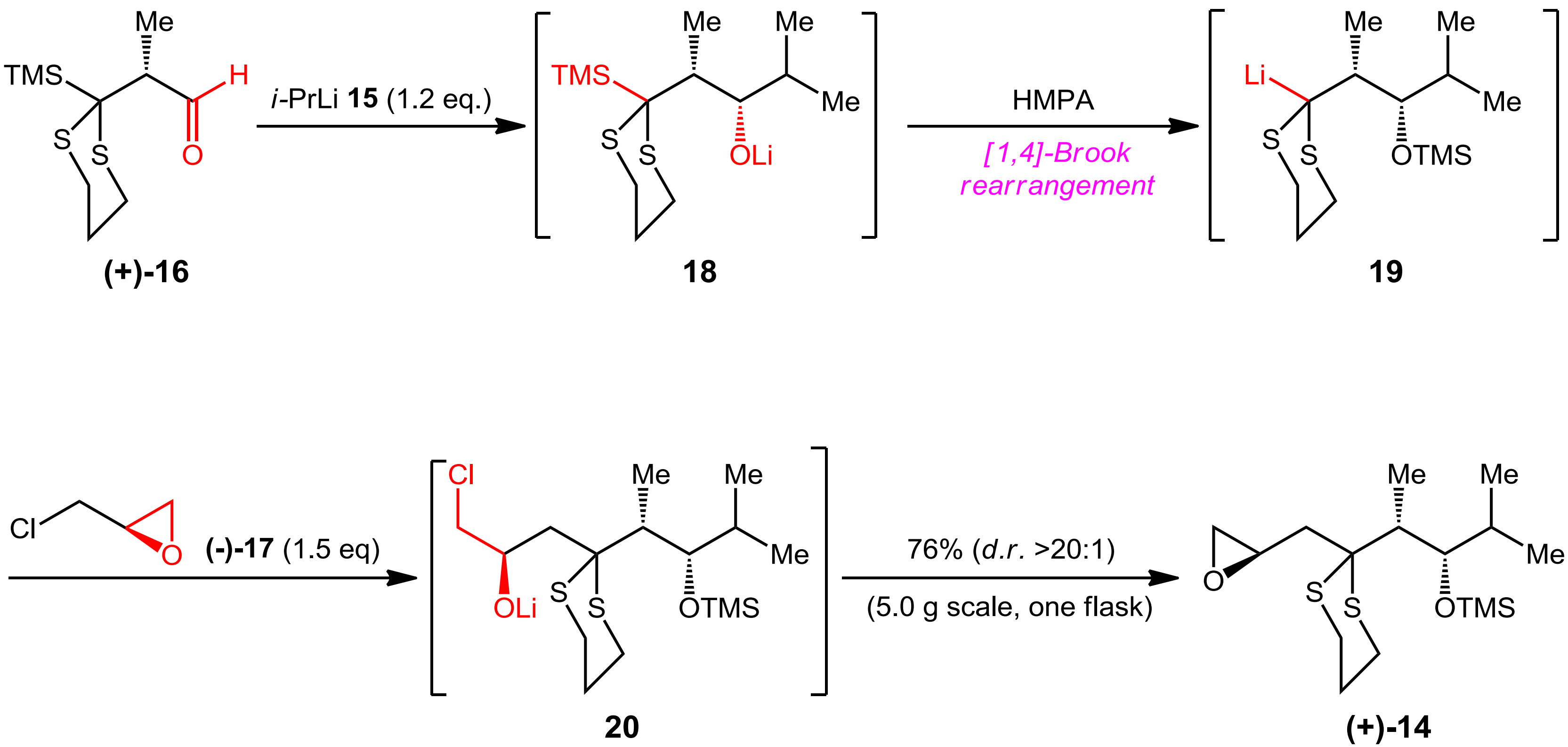




Synthesis of Side Chain (+)-9



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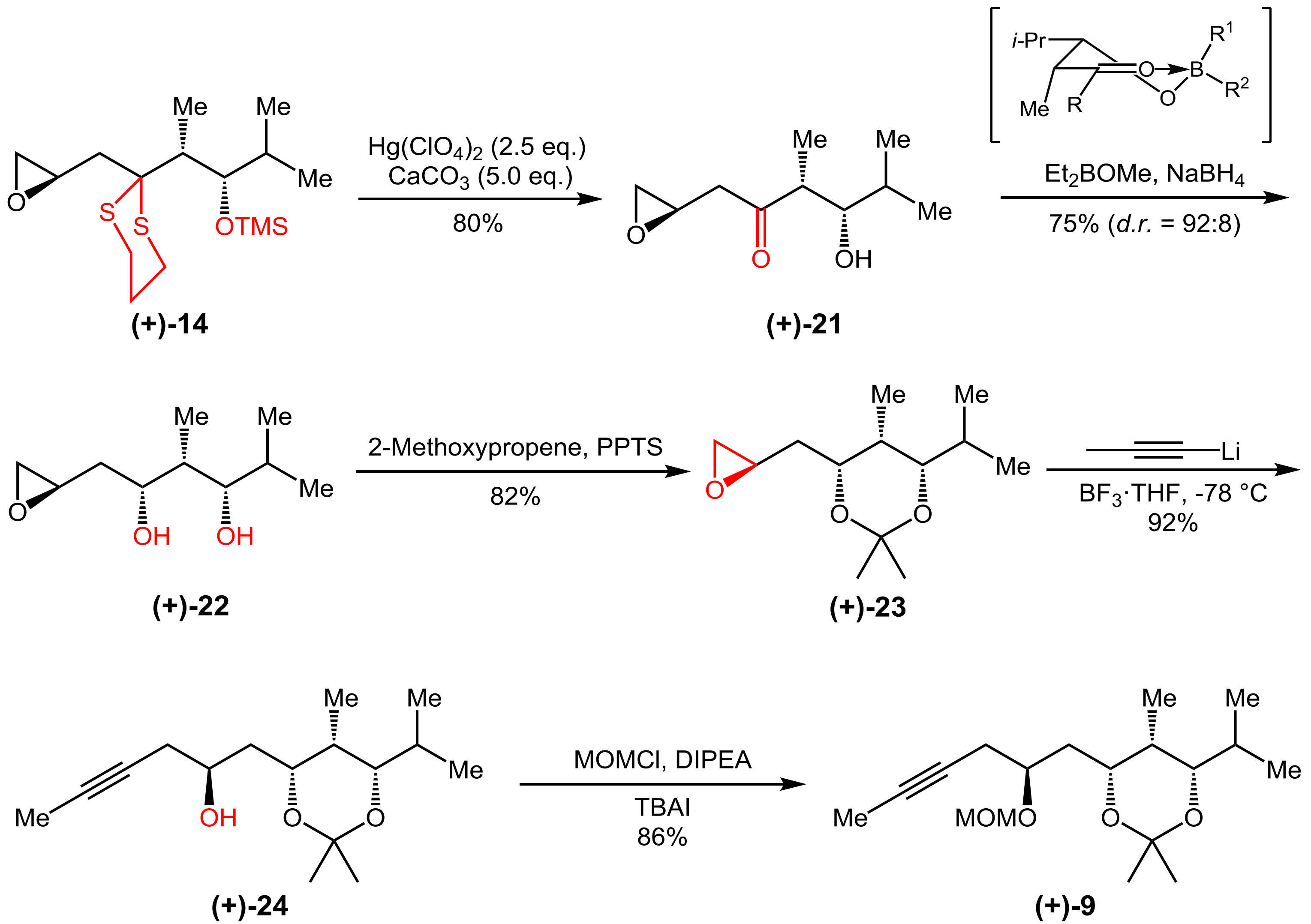
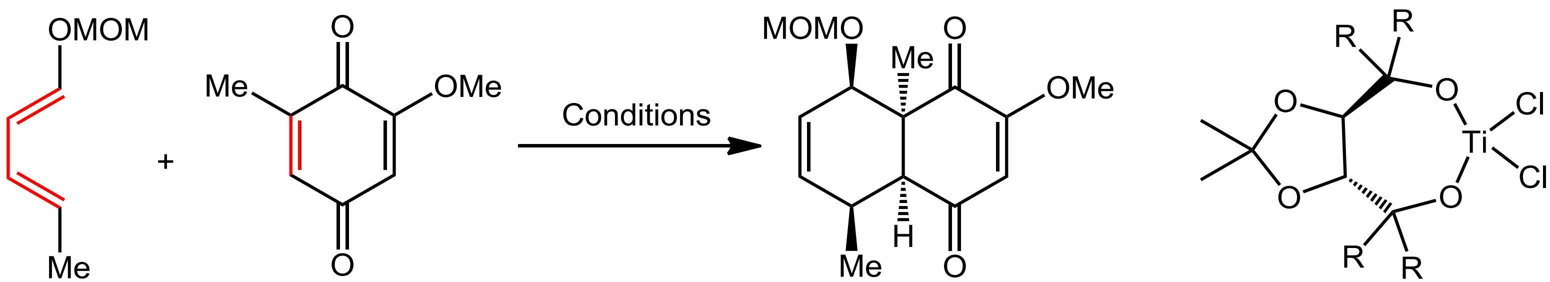


Asymmetric Diels-Alder Reaction



13 **12** **11**

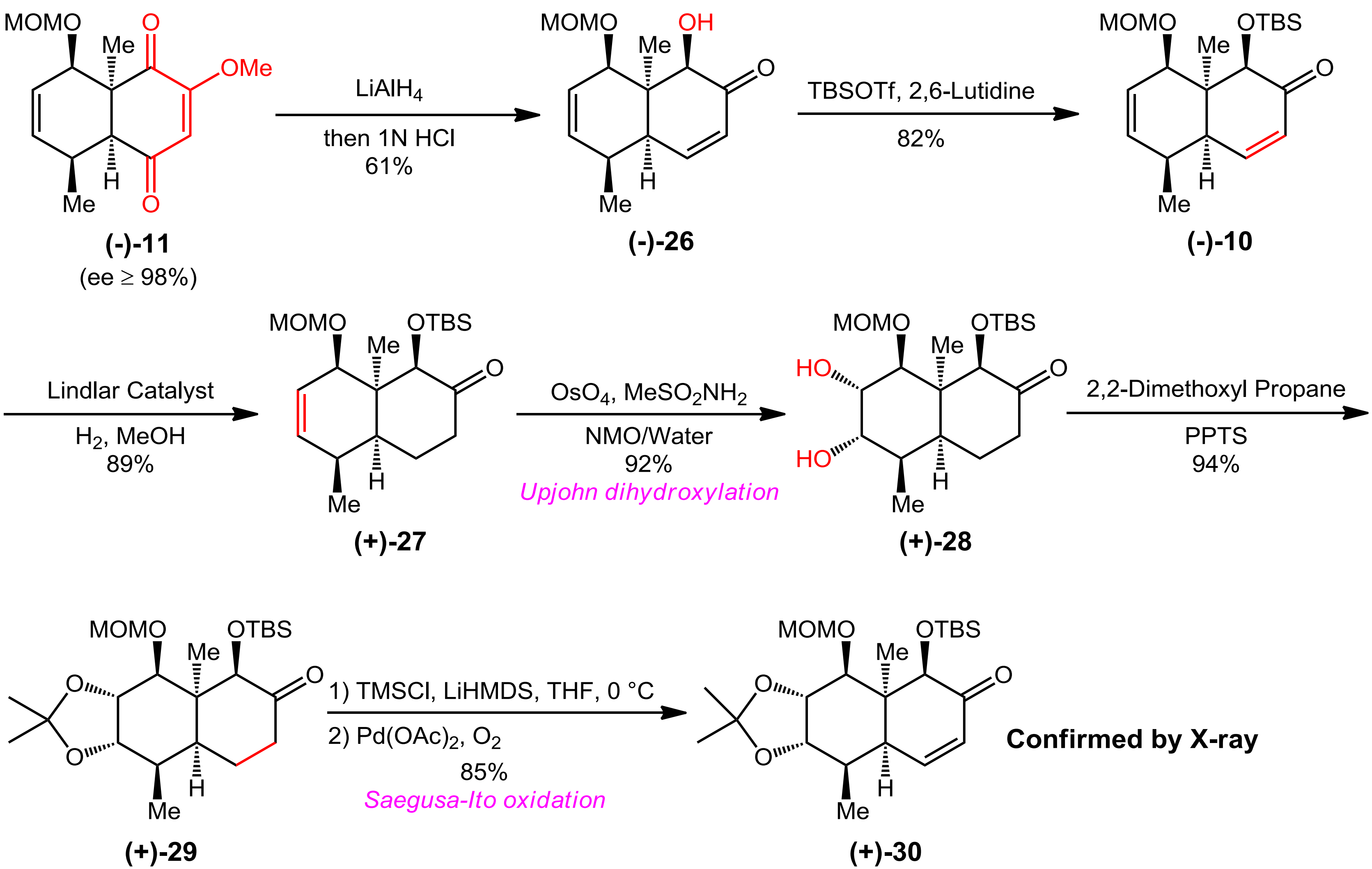
Confirmed by X-ray

R = 1-naphthyl

Ti-complex (-)-**25**

Entry	Conditions	Yield	Ee
1	Toluene/CH_2Cl_2, 120 ºC, 48 h	74	0
2	1 eq. **25**, CH_2Cl_2, -40 ºC, 24 h	71	73
3	20 mol% **25**, CH_2Cl_2, 0 ºC to rt, 24 h	25	55
4	20 mol% **25**, 4 Å MS, CH_2Cl_2, -60 ºC, 12 h	80	71
5	20 mol% 25, 4 Å MS, Toluene, -78 ºC to -40 ºC, 42 h	95	86

Synthesis of *cis*-Decalin (+)-8



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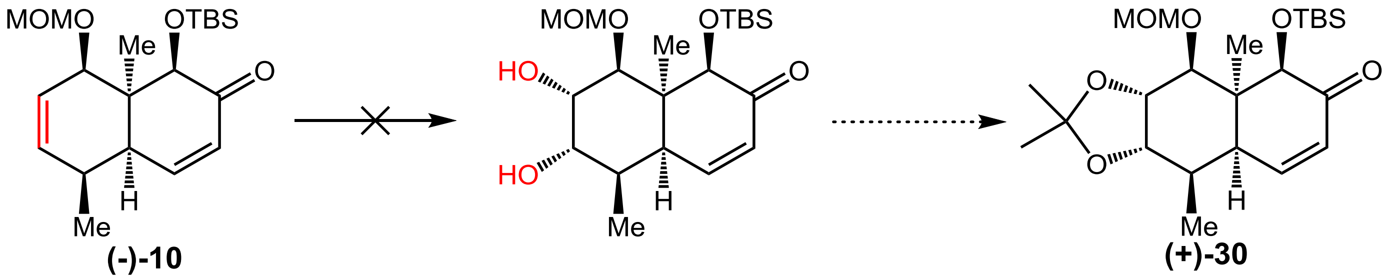

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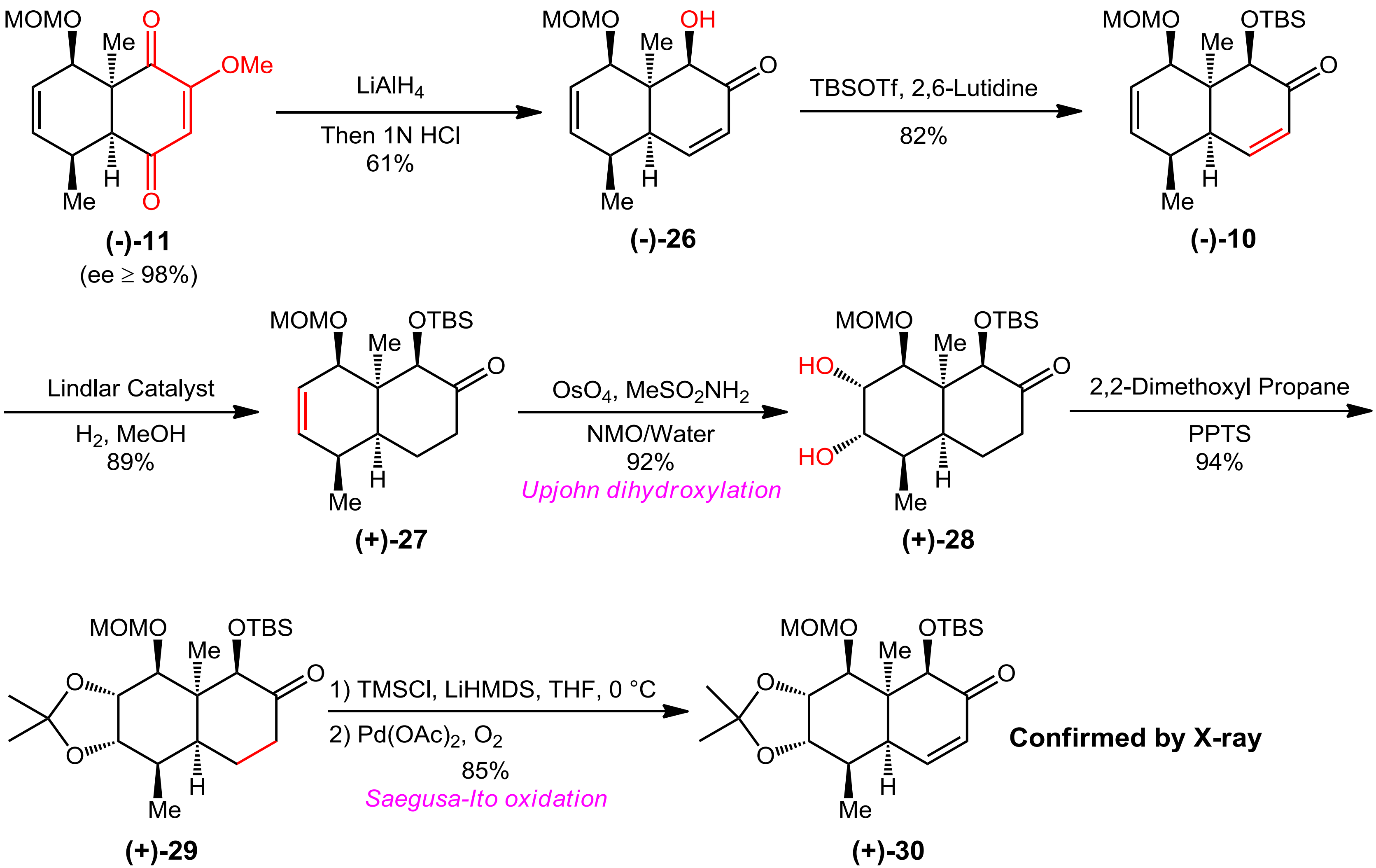
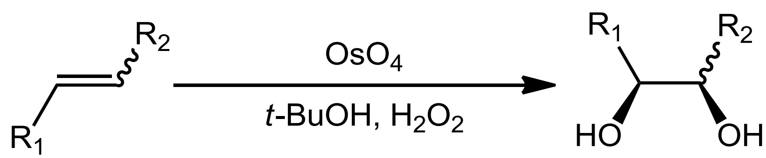
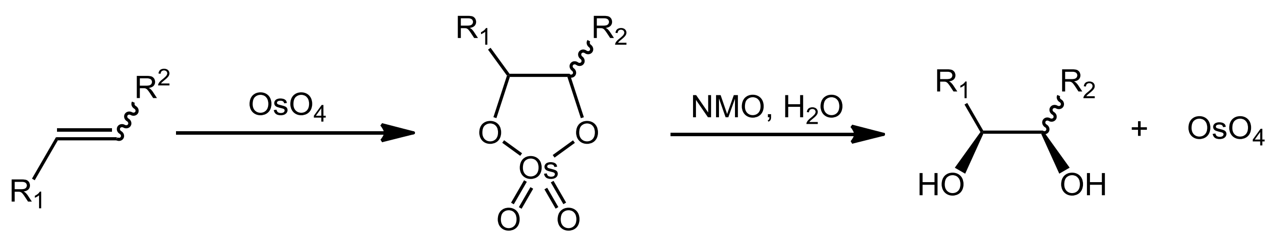


Dihydroxylation Reactions

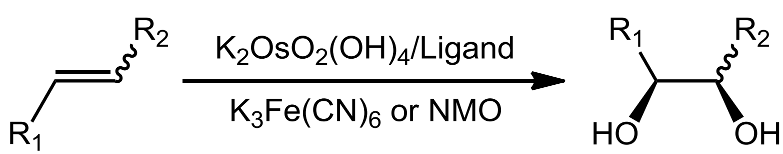
Milas Hydroxylation



Upjohn Dihydroxylation

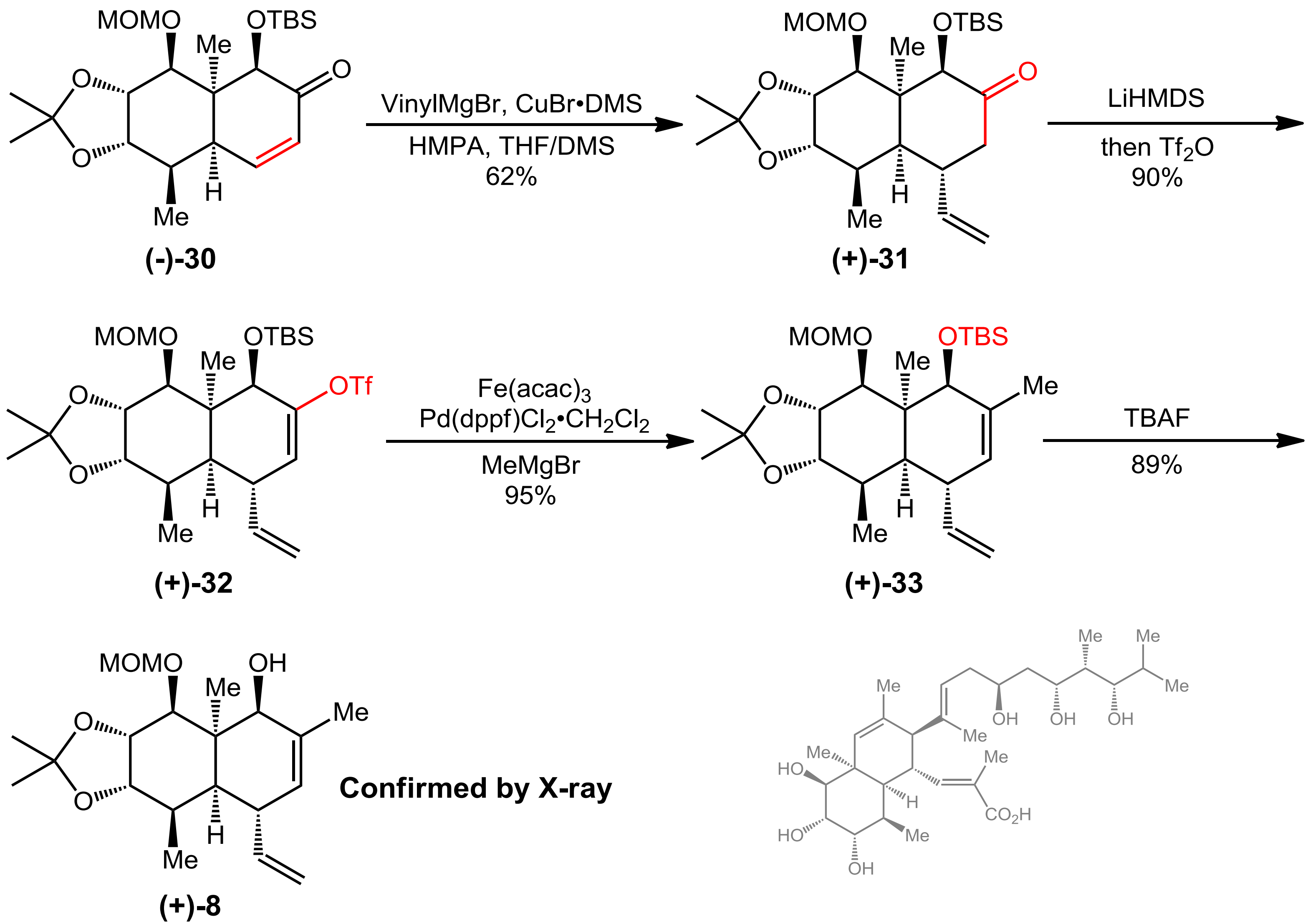


Sharpless Asymmetric Dihydroxylation

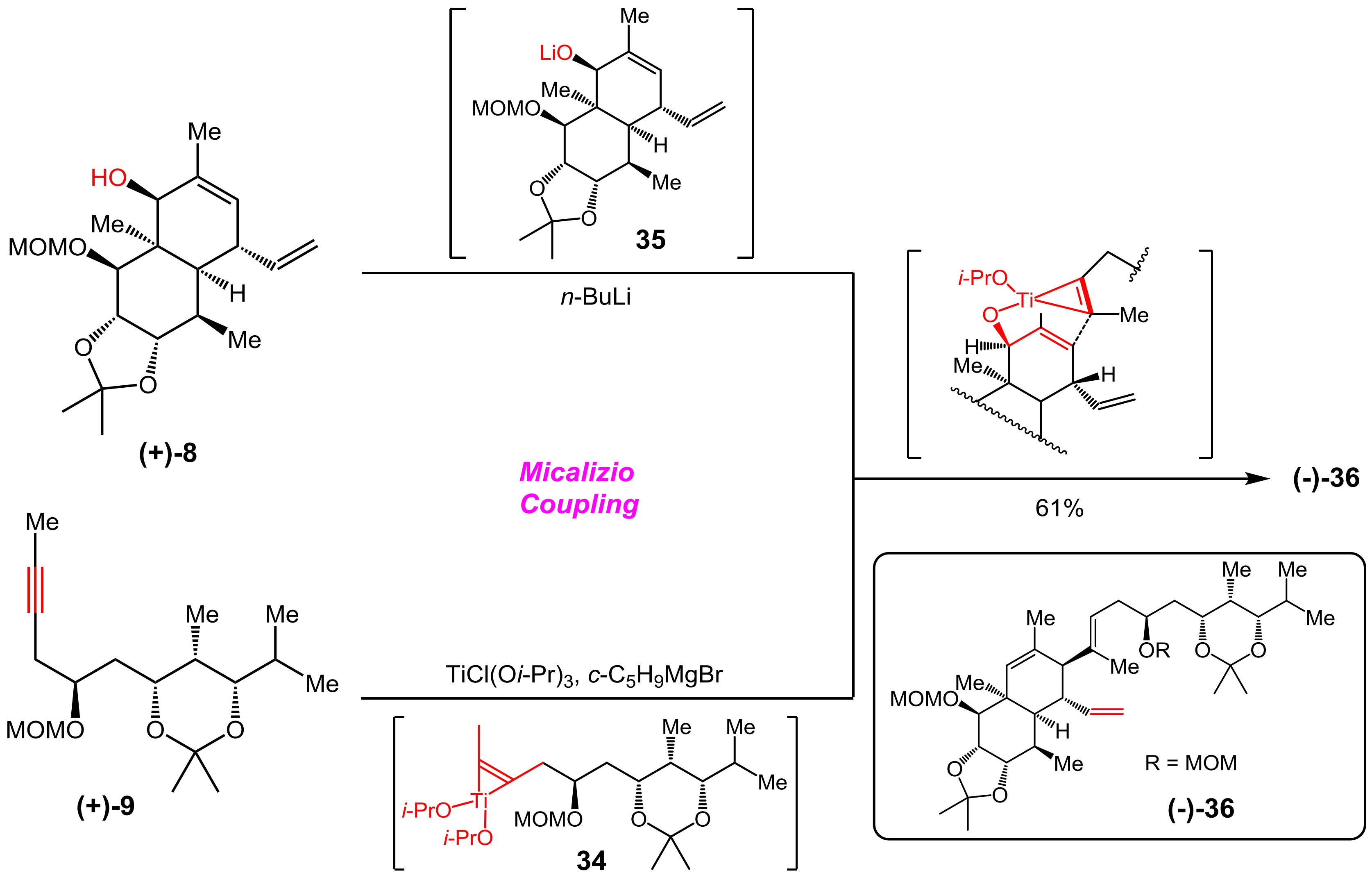


Drawback: *cis*-alkenes, low enantioselectivity

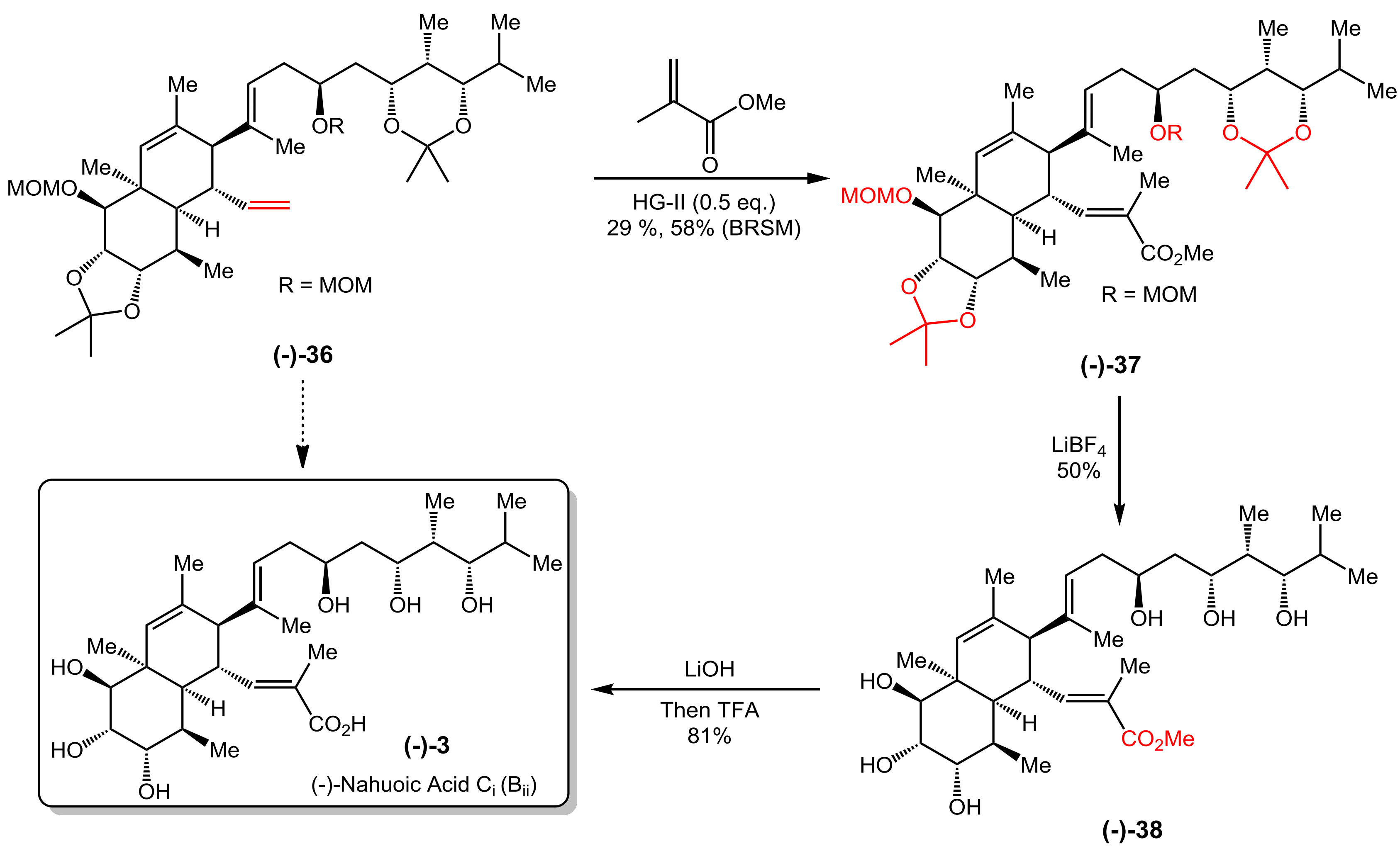
Synthesis of *cis*-Decalin (+)-8



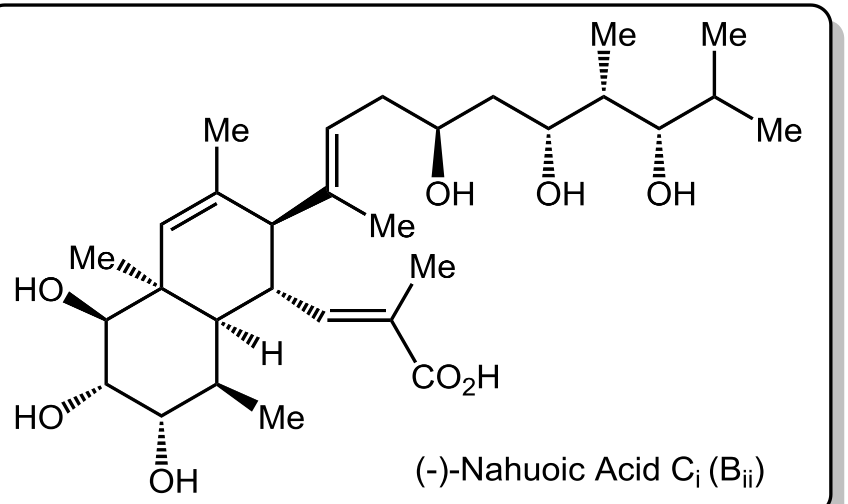
Hydroxyl-Directed Alkyne-Alkene Coupling



Synthesis of (-)-Nahuoic Acid C_i (B_{ii})



Summary



(-)-Nahuoic Acid C_i (B_{ii})

- The first total synthesis;
- 16 steps (the longest linear sequence), 0.39% overall yield;
- Type II anion relay chemistry (ARC);
- Ti-catalyzed asymmetric Diels-Alder reaction;
- Micalizio alkoxide-directed alkyne-alkene tactic.

The First Paragraph

Nahuoic acid A, isolated by Anderson and co-workers in 2013 from a culture of a Stremptomyces sp. obtained from a tropical marine sediment, displays selective (*S*)-adenosylmethionine (SAM)-competitive inhibitor activity against the histone lysine methyltransferase SETD8 enzyme. In 2016, the same group reported the isolation of nahuoic acids B_i-E_i, which exhibit similar inhibitory effects on SETD8. In the same year, the Qi group independently reported the isolation of four related congeners, the nahuoic acids B_{ii}-E_{ii}, leading to a total of seven members of this architecturally intriguing family of polyketide acids. Herein, we reported the first total synthesis of a member of the nahuoic acid family, namely C_i (B_{ii}).

The Last Paragraph

In summary, we have achieved the first total synthesis of a member of the nahuoic acid family of *cis*-decalin-containing polyketides, namely C_i (B_{ii}), in a longest linear sequence of 16 steps. Highlights of the synthesis include Type II Anion Relay Chemistry (ARC) to construct the polyol chain, a Ti-catalyzed asymmetric Diels−Alder reaction to generate the *cis*-decalin skeleton in a highly enantiomerically enriched form, and a late-stage strategic large fragment union *via* the Micalizio alkoxide-directed alkyne−alkene tactic. Studies toward the synthesis of other members of the nahuoic acid family, as well as the development of analogues for biological evaluations, continue in our laboratory.

Acknowledgement

Thanks
for your attention