Literature Report V

Total Syntheses of Alcyonolide, (+)-Waixenicin A, and (−)-Xeniafaraunol A

Reporter: Gao-Wei Wang
Checker: Li-Xia Liu
Date: 2023-07-03

Steinborn, C.; Huber, T.; Lichtenegger, J.; Plangger, I.; Wurst, K.;

Magauer, T. *J. Am. Chem. Soc.* **2023**, *145*, 11811

CV of Prof. Thomas Magauer

Research:

- Total Synthesis of Natural Product
- Natural Product Chemistry
- C–H Bond Activation
- High-Pressure Chemistry
- Medicinal Chemistry

Background:

- **2002-2007** B.S., University of Vienna, Vienna, Austria (Advisor: Prof. J. Mulzer)
- **2007-2009** M.S., University of Vienna, Vienna, Austria (Advisor: Prof. J. Mulzer)
- **2010-2012** Ph.D., Harvard University, Cambridge, USA (Advisor: Prof. A. G. Myers)
- **2012-2017** Assistant Professor, Ludwig Maximilian University of Munich, Munich, Germany
- **2017-Now** Full Professor, Leopold-Franzens University of Innsbruck, Innsbruck, Austria

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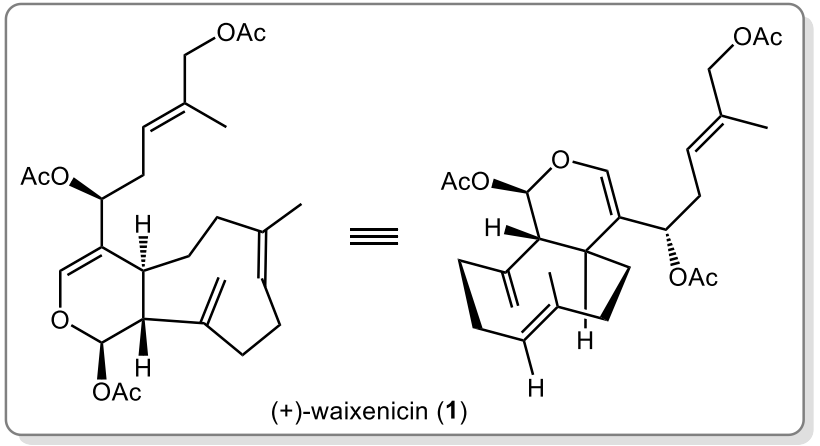
Introduction

Sarcothelia edmondsoni (软珊瑚)



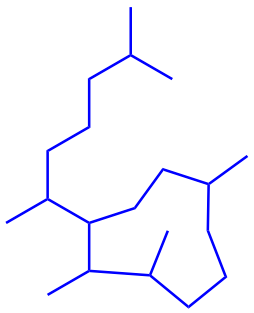
Waixenicin A (怀西尼辛A)

- ***trans*-Fused oxabicyclo[7.4.0]tridecane ring system**
- **Four stereogenic centers and two allylic acetates**
- **Enol acetal and 9-memberd ring**
- **First isolation from *Sarcothelia edmondsoni* by Scheuer and Clardy in 1984**

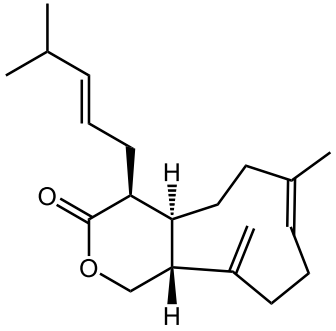
Coval, S. J.; Scheuer, P. J.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1984**, *40*, 3823

Introduction

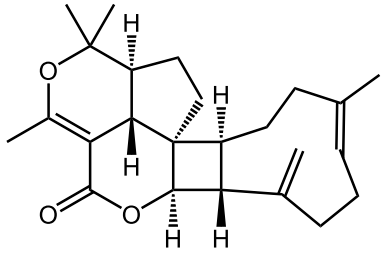
General features and selected structures of *Xenia* diterpenoids



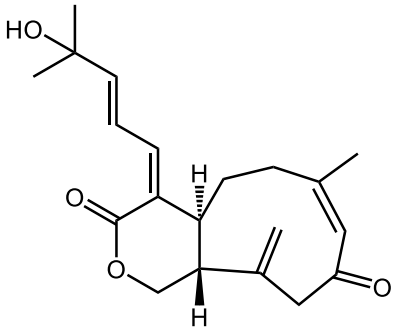
xenicane skeleton



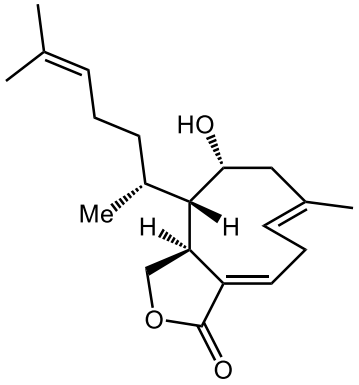
coraxeniolide A (**2**)
[Leumann 2000, Corey 2008]



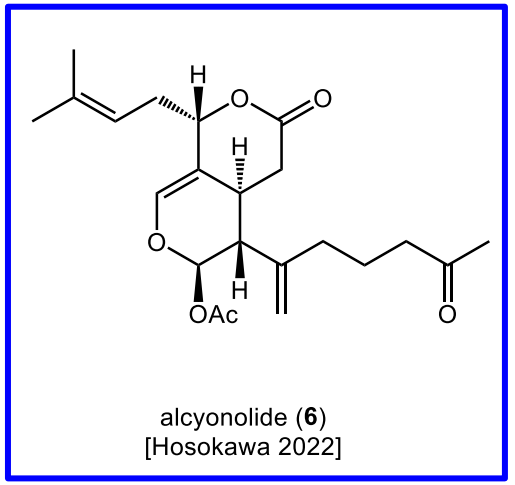
antheliolide A (**3**)
[Corey 2006]



blumiolide C (**4**)
[Altmann 2008]

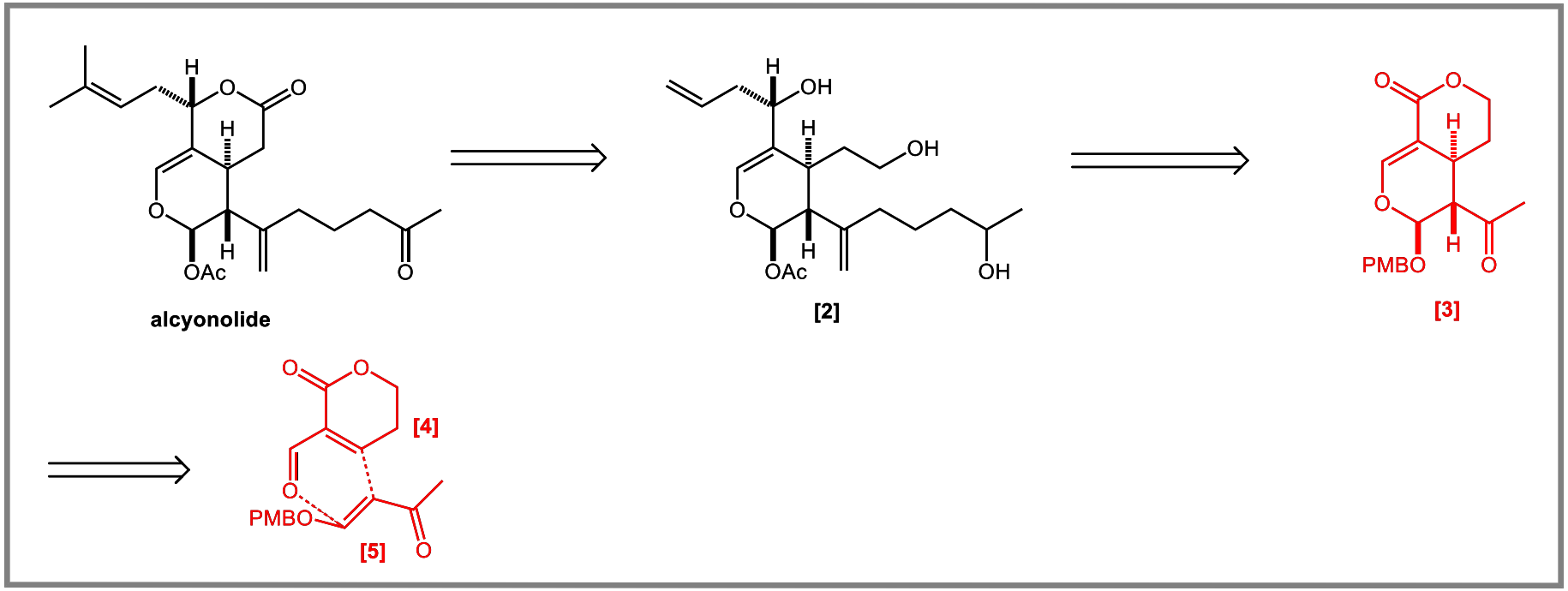


4-hydroxydictyolactone (**5**)
[Williams 2009]

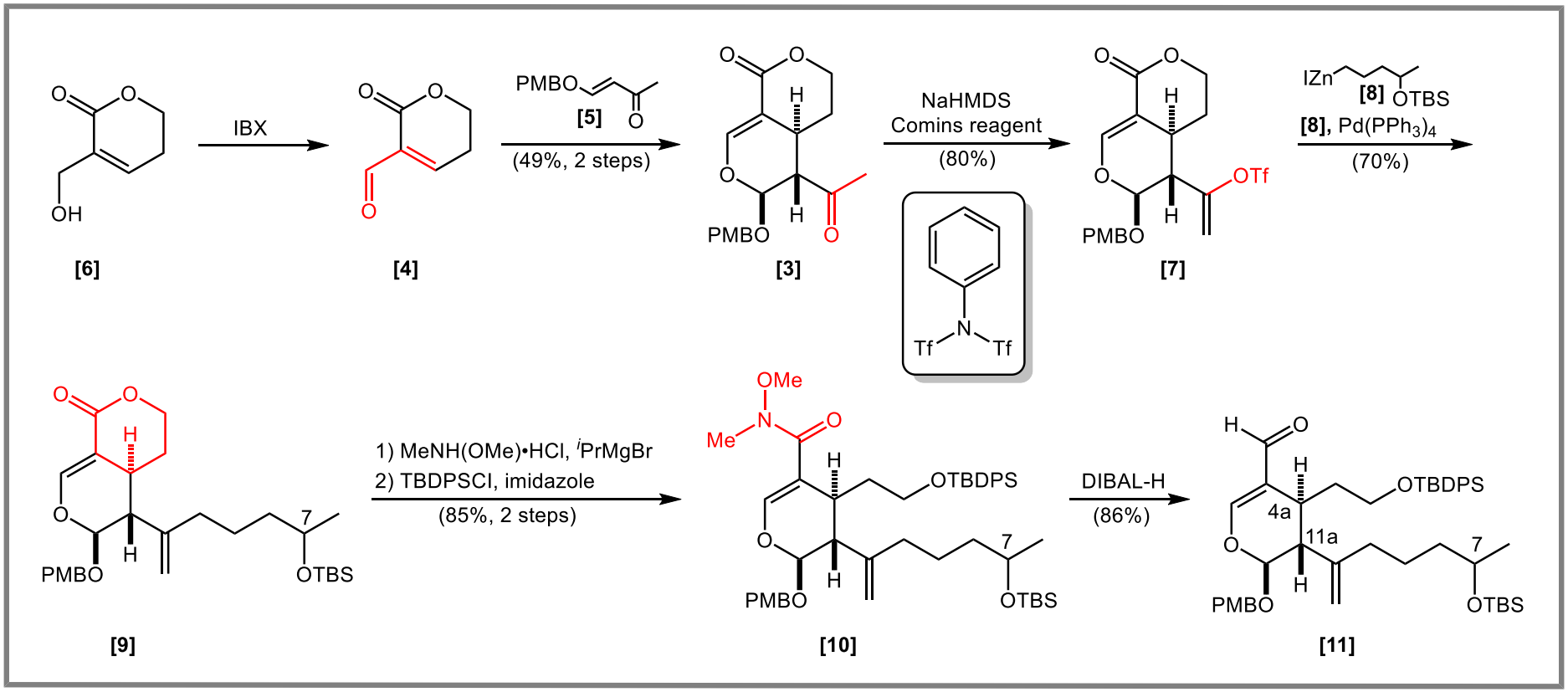


alcyonolide (**6**)
[Hosokawa 2022]

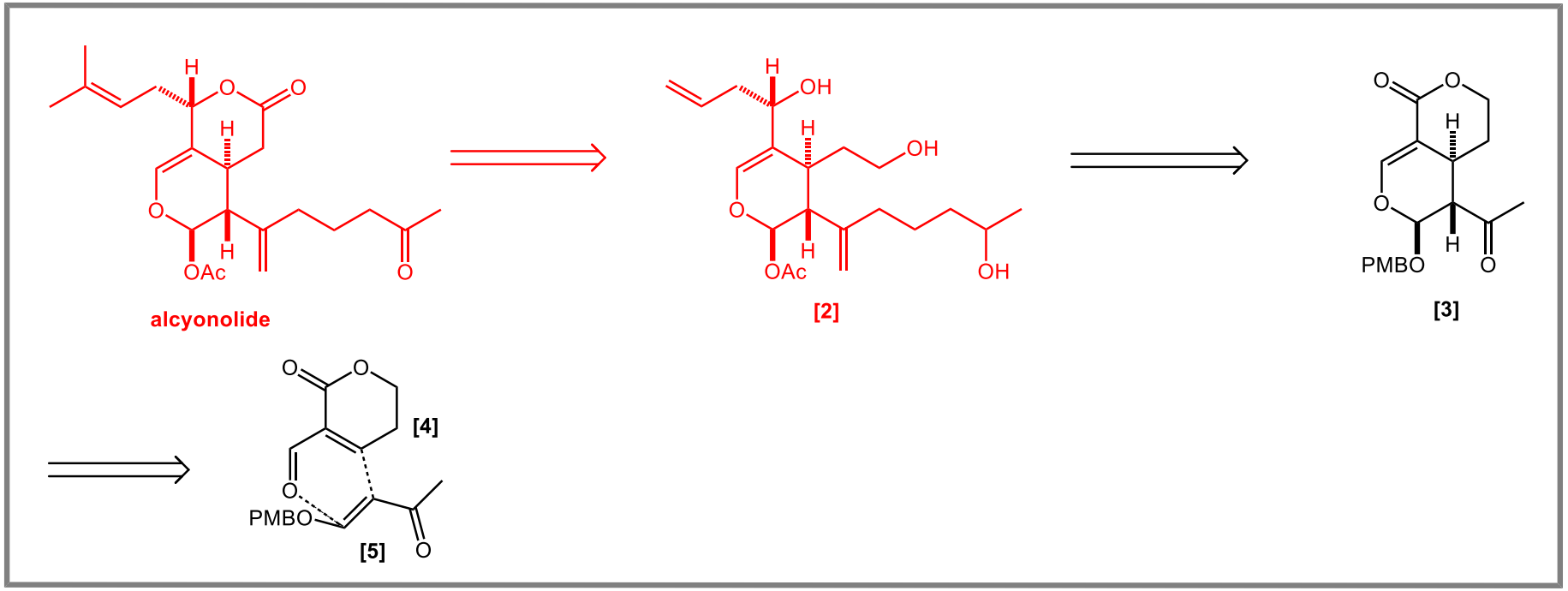
Retrosynthetic Strategy



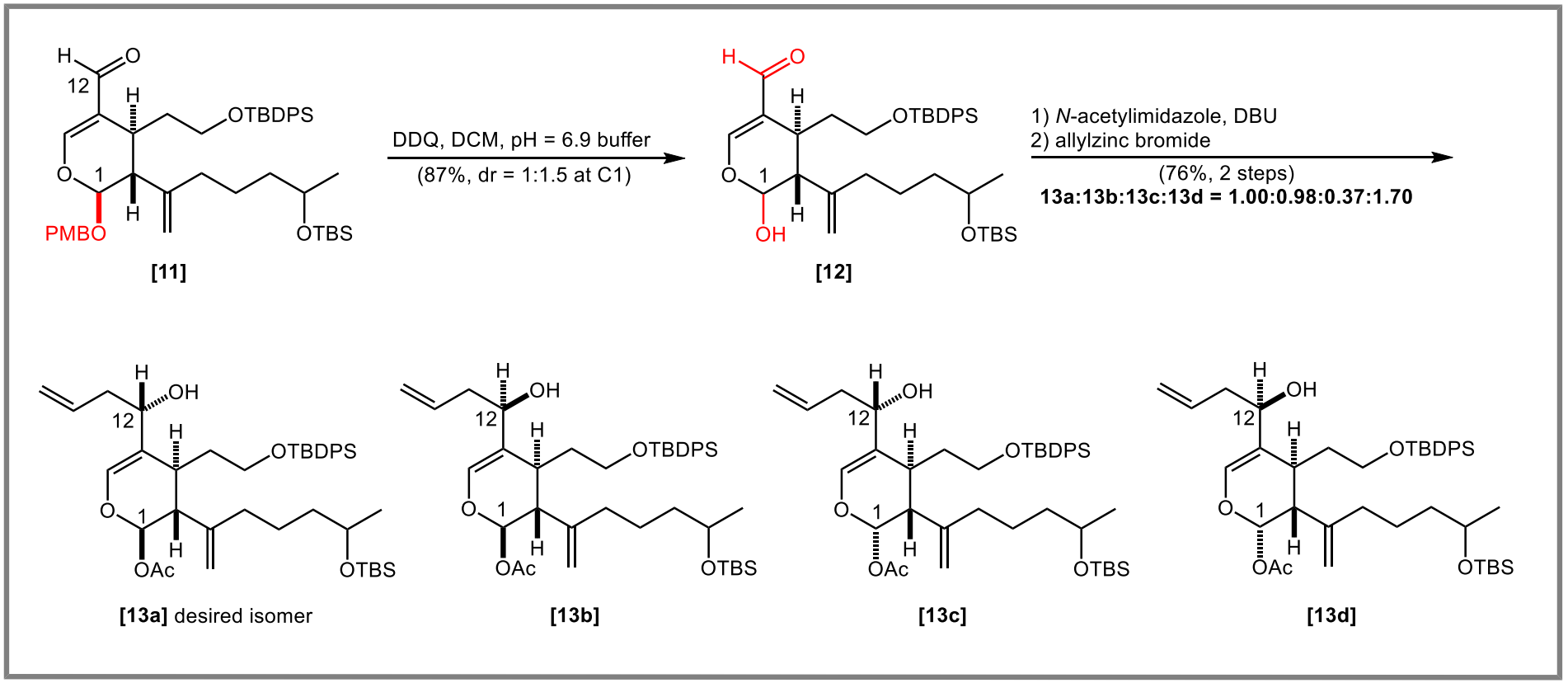
Synthesis of Formyldihydropyran [11]



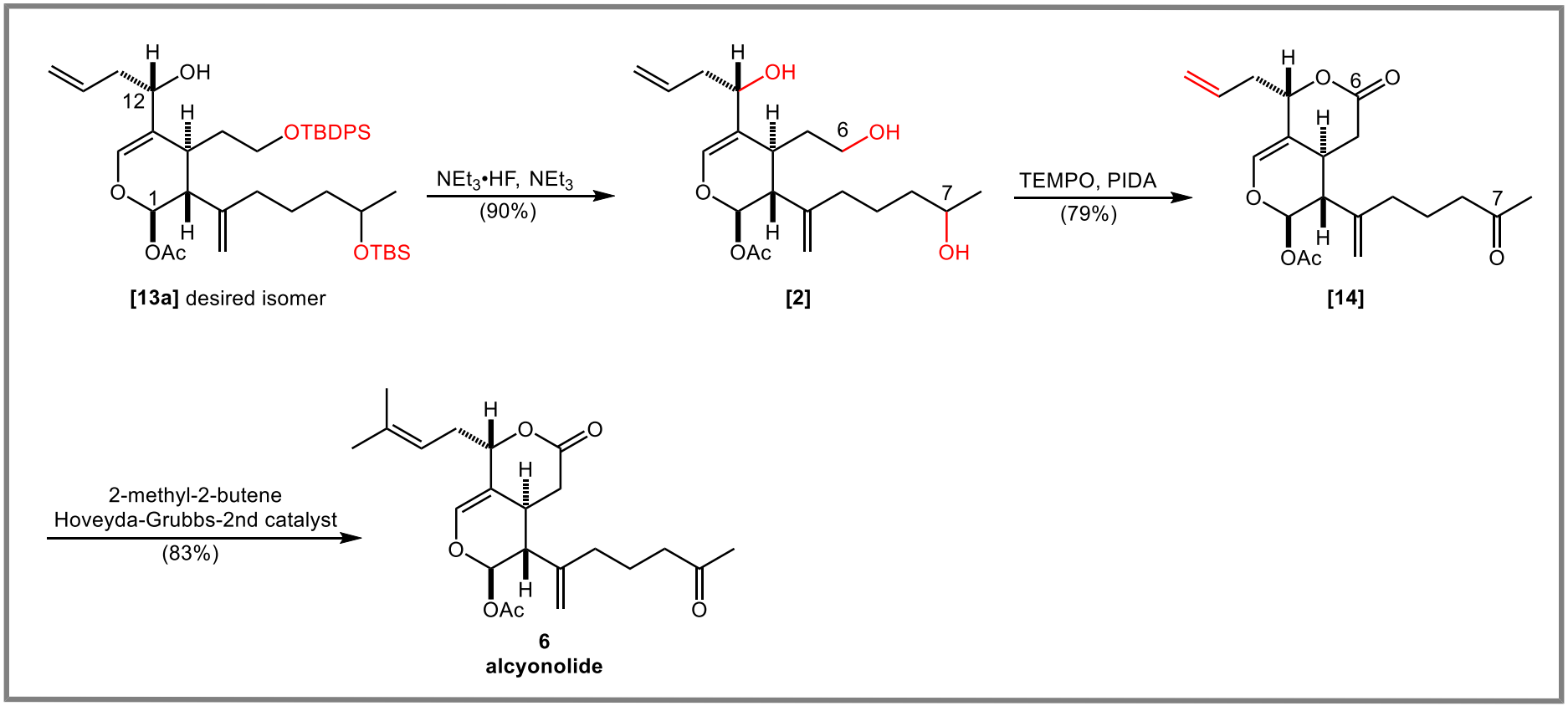
Retrosynthetic Strategy



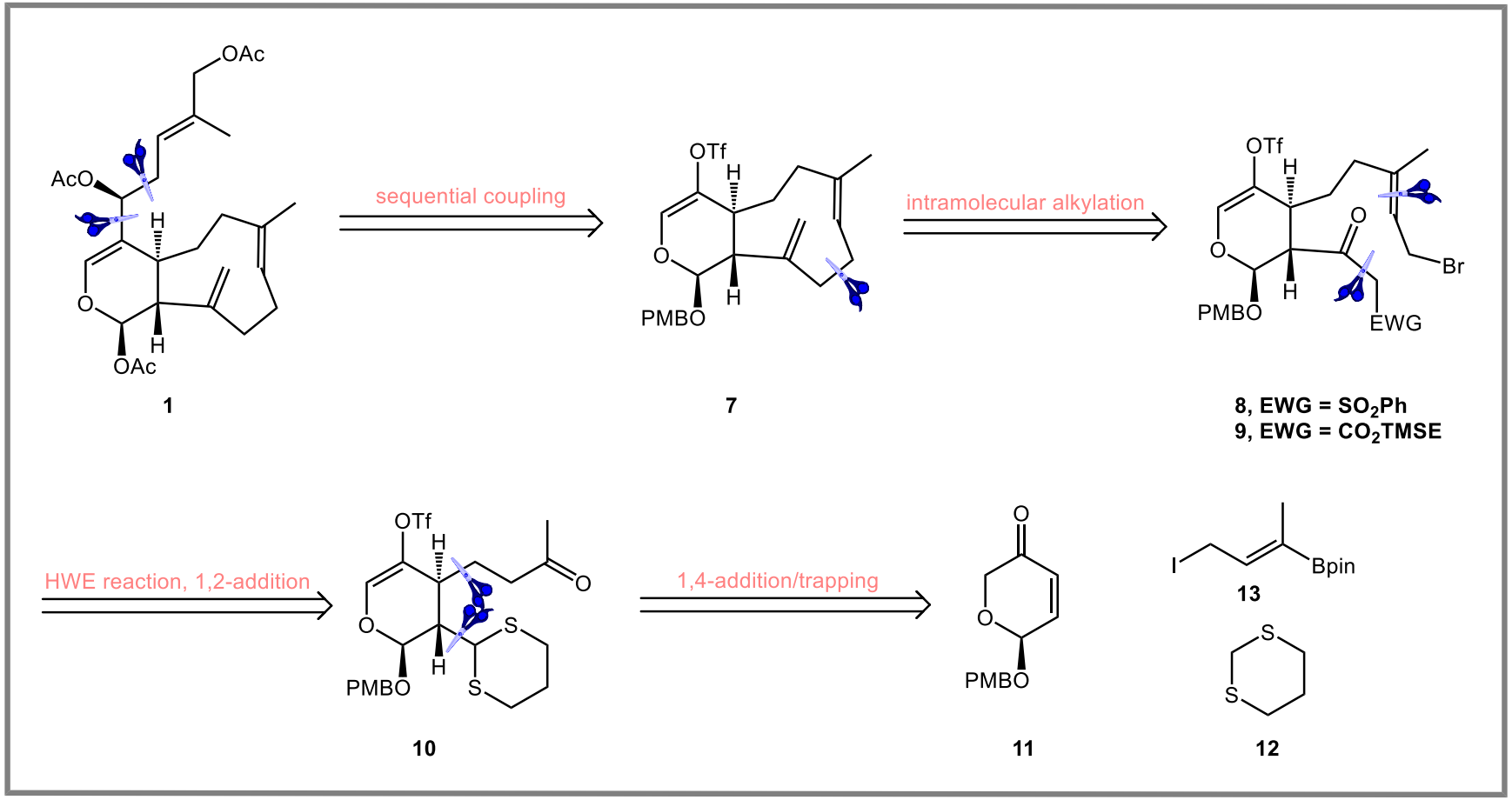
Transformation at C1 and C12 Positions



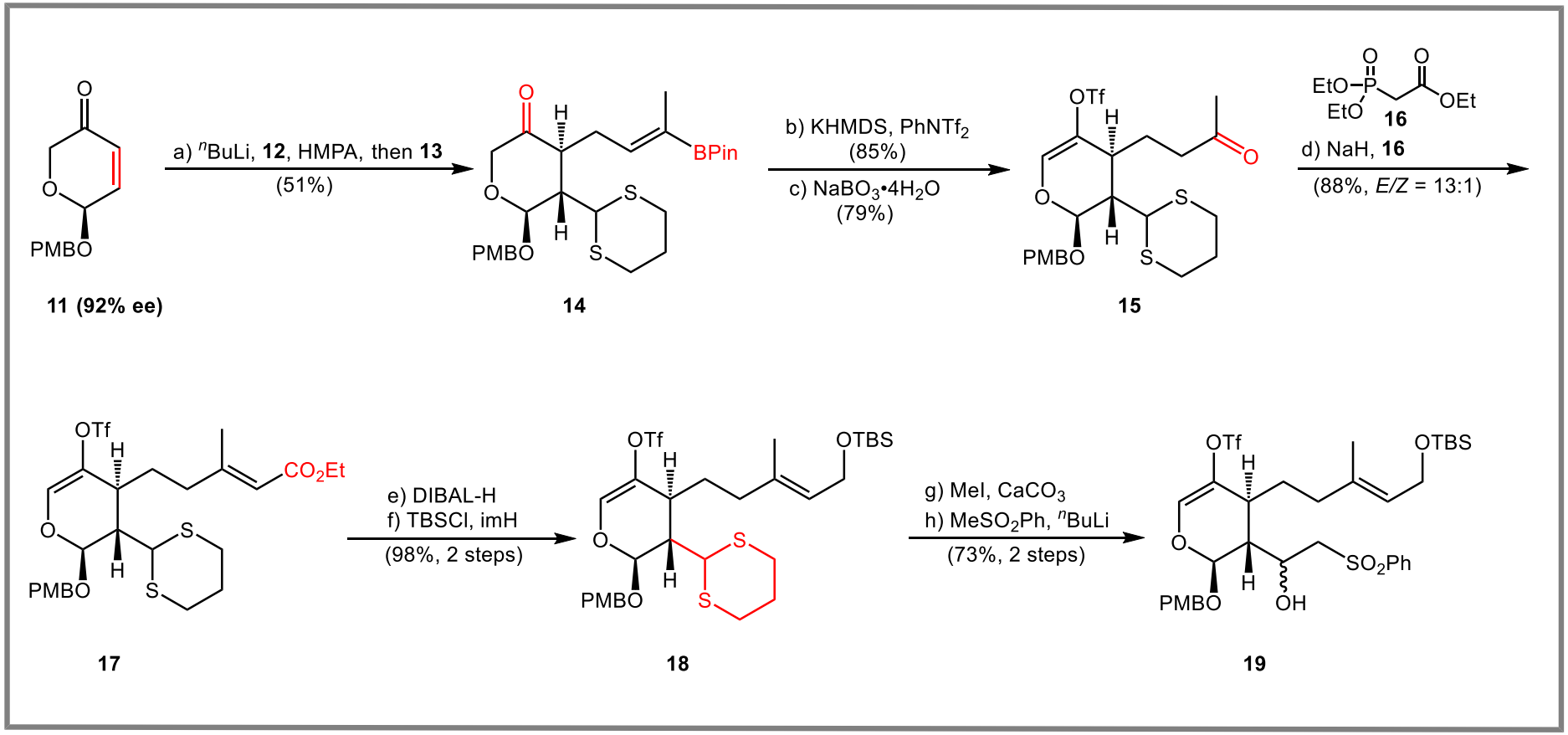
Synthesis of Alcyonolide



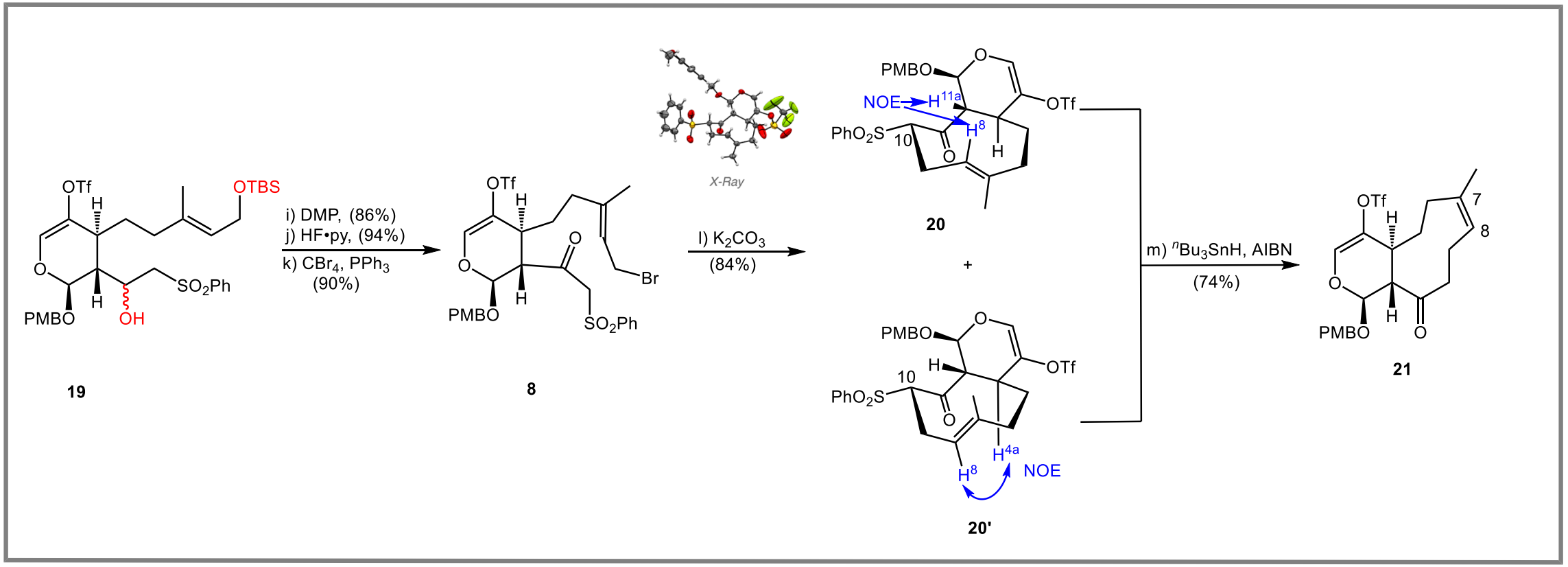
Retrosynthetic Strategy



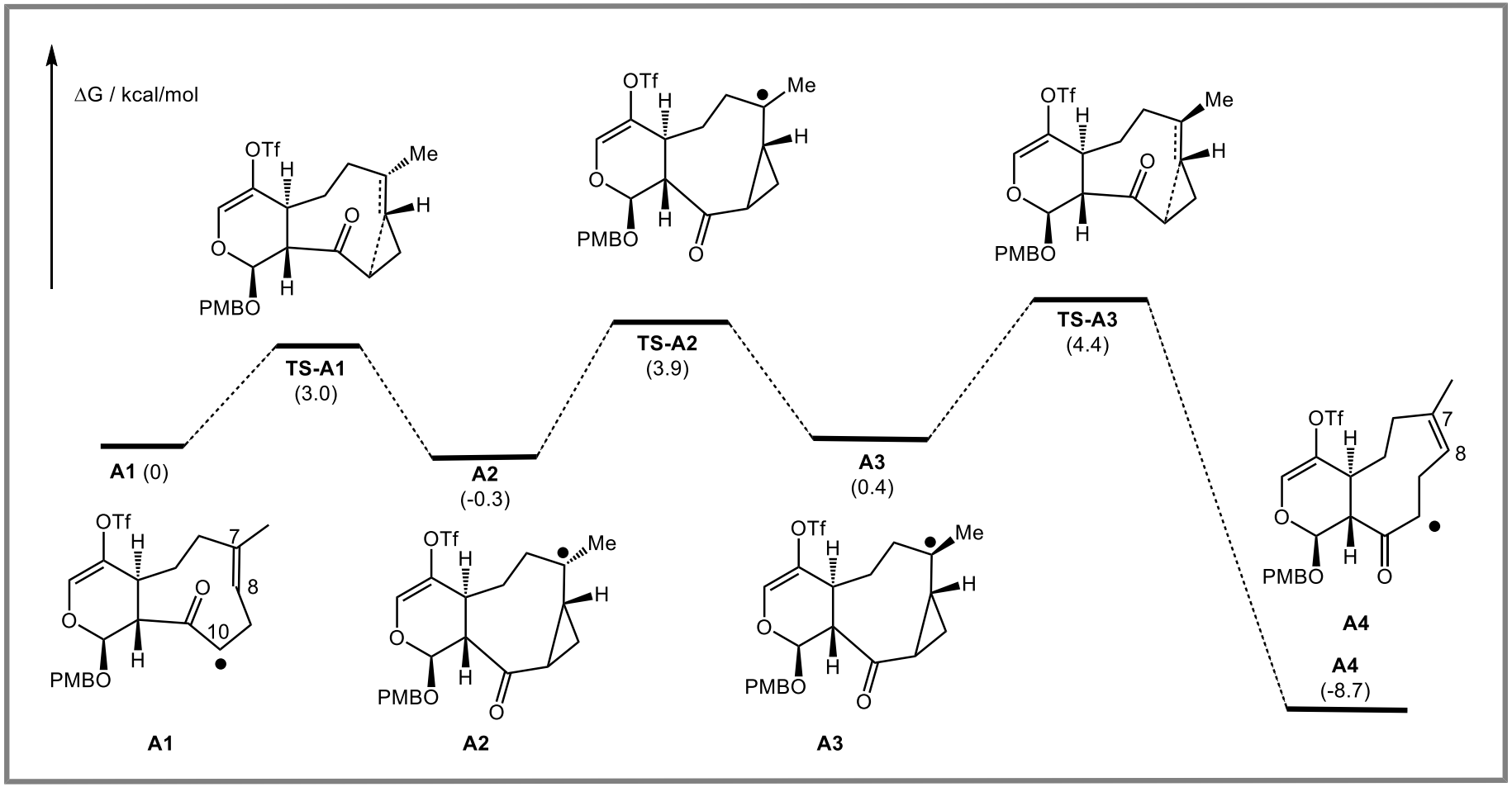
Synthesis of Intermediate 19



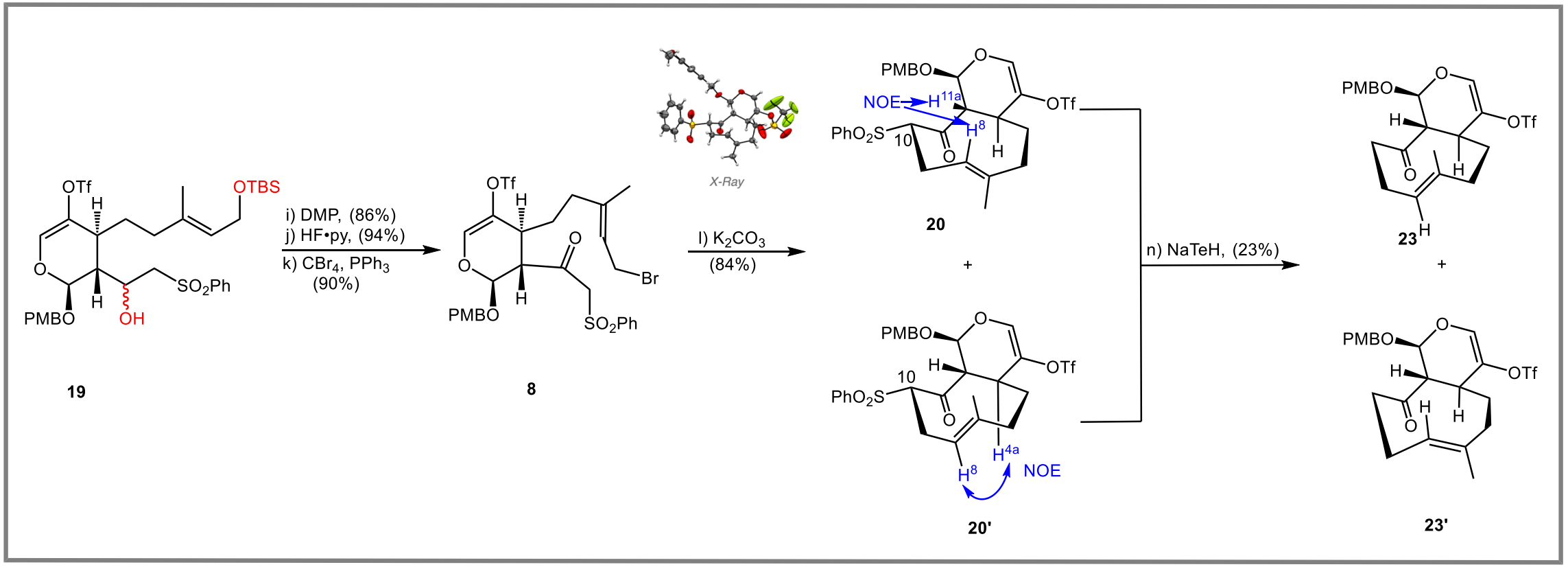
Synthesis of Intermediate 21



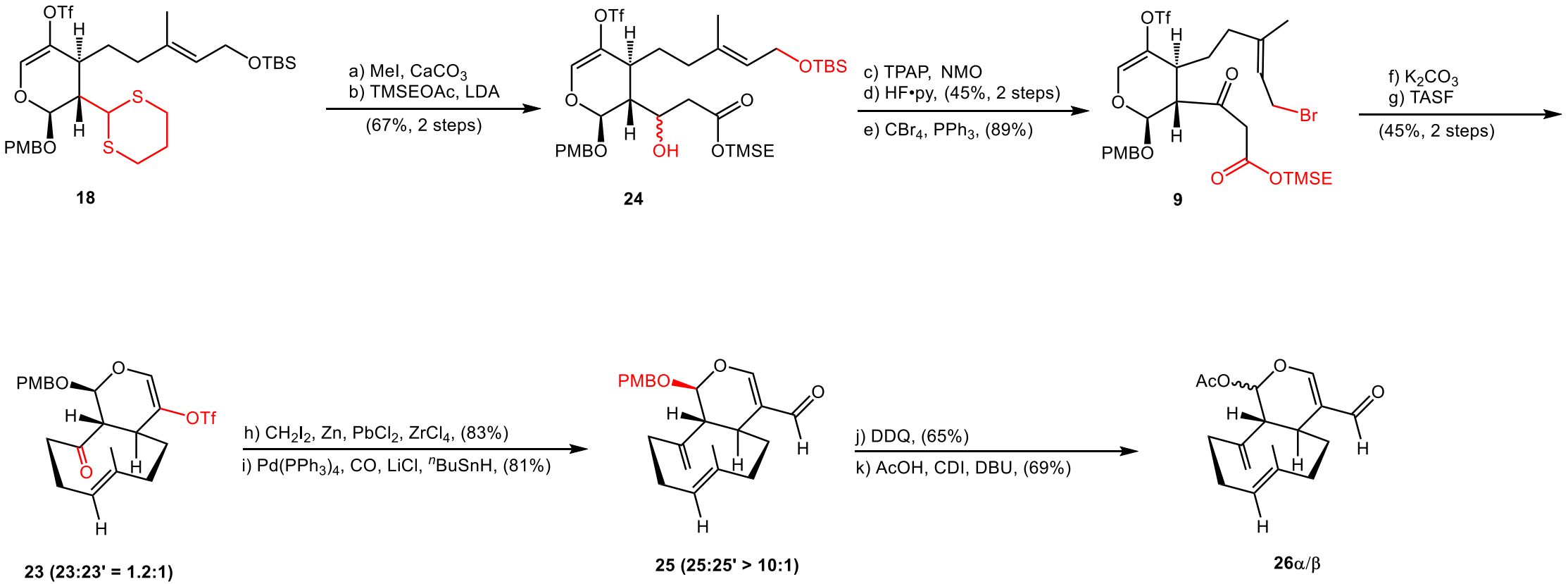
Isomerization of the C7/C8-Alkene



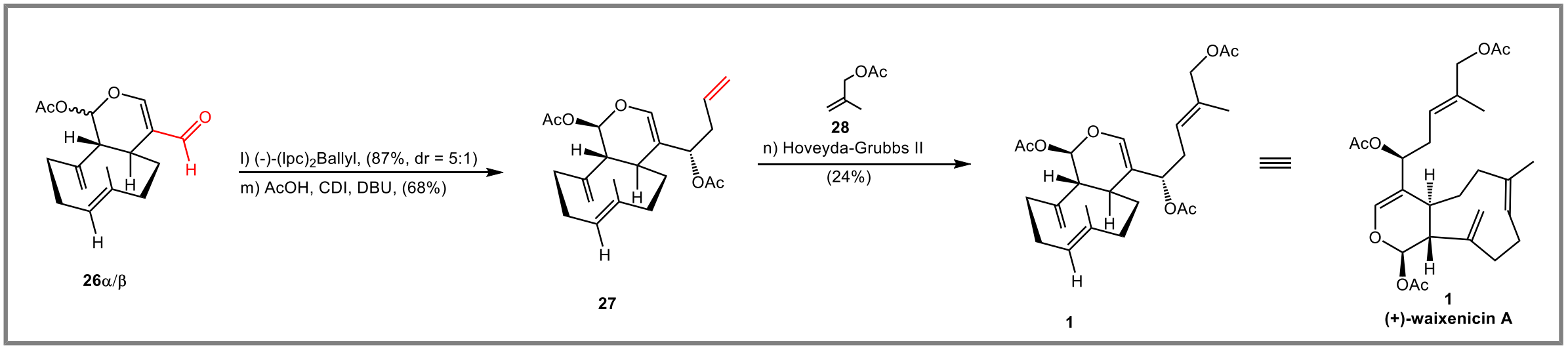
Synthesis of Intermediate 23



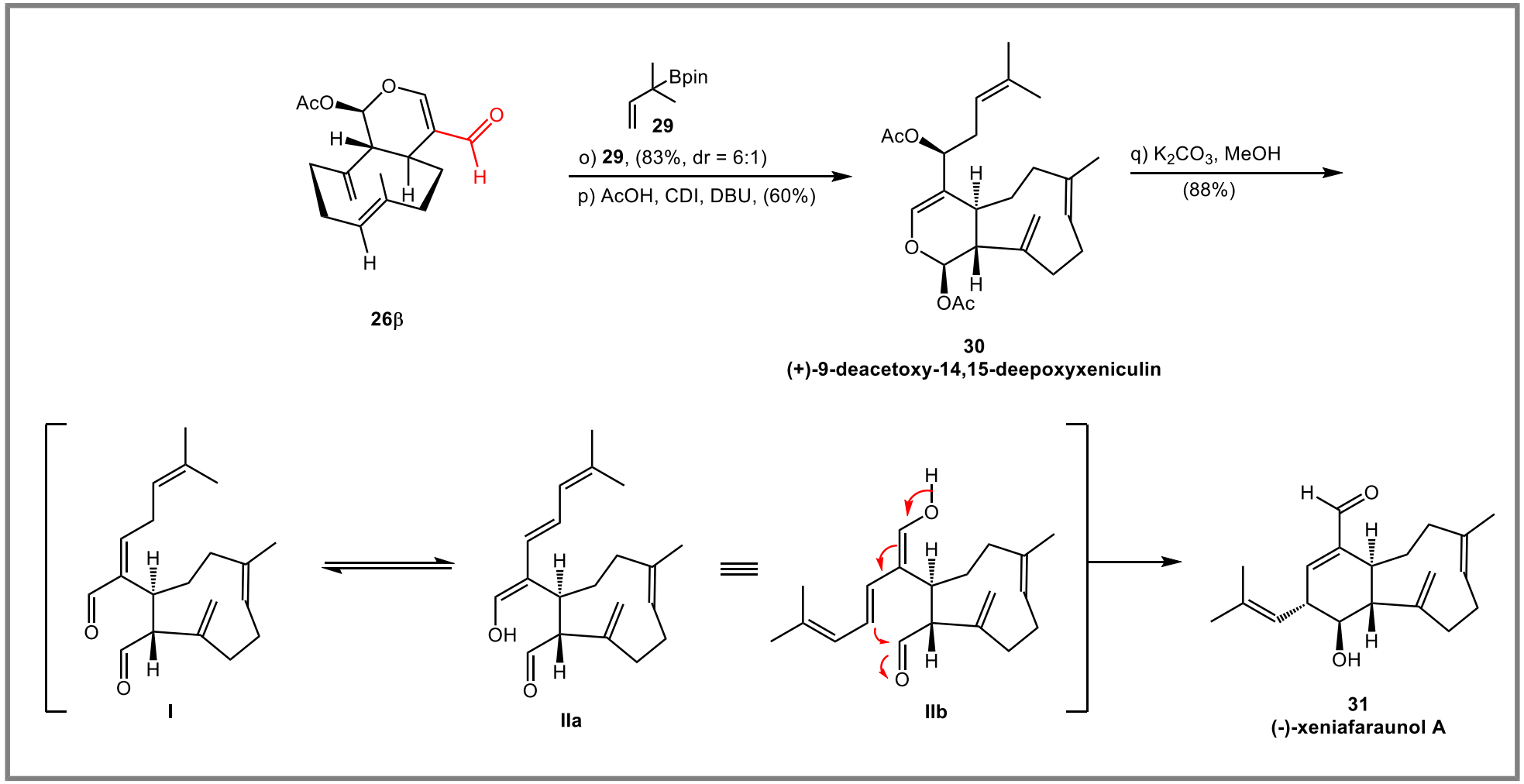
Synthesis of Intermediate 26



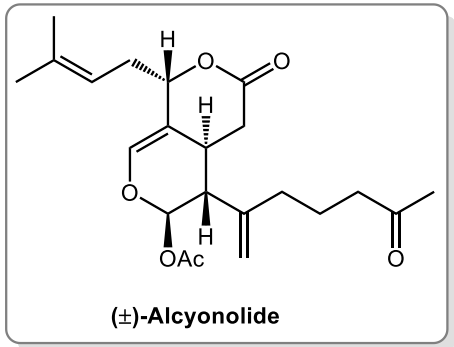
Synthesis of (+)-Waixenicin A



Synthesis of (-)-Xeniafaraunol A

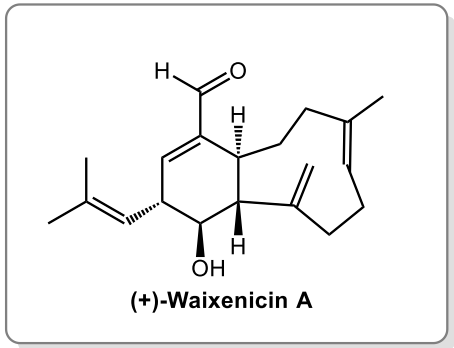


Summary



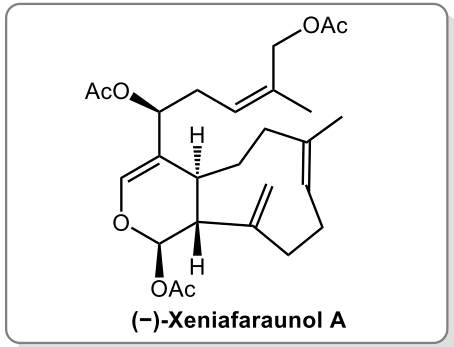
(±)-Alcyonolide

- ✓ Inverse electron demand hetero Diels−Alder reaction
- ✓ Zinc-mediated C−C bond formation reactions
- ✓ Overall 7.8% yield, 13 steps



(+)-Waixenicin A

- ✓ A highly diastereoselective conjugate addition/trapping sequence was employed
- ✓ The 9-membered carbocycle was constructed by intramolecular alkylation reaction



(−)-Xeniafaraunol A

- ✓ A high-yielding base-mediated dihydropyran-cyclohexene rearrangement of 30 led to xeniafaraunol A in one step
- ✓ Overall 0.15% yield, 20 steps for (+)-waixenicin A; Overall 0.47% yield, 20 steps for (-)-xeniafaraunol A

Writing Strategy

☐ The First Paragraph

waixenicin A 的发现
及其生物活性

该类天然产物
的研究现状

研究的意义
引出本文工作

- ✓ In 1984, Scheuer and Clardy reported the isolation of waixenicin A (1) from an extract of the marine soft coral *Sarcothelia edmondsoni* harvested along the Hawaiian coast. 1 stands out due to its unique biological profile and has been intensively investigated for its potential to act as a specific inhibitor of TRPM7 channels.
- ✓ To date, only the total syntheses of coraxeniolide A, antheliolide A, blumiolide C, the related *Dictyo* diterpenoid 4-hydroxydictyolactone, and *seco*-xenicin alcyonolide have been accomplished.
- ✓ Their synthesis has remained elusive for more than four decades. Here, we report the total synthesis of (+)-waixenicin A and (+)-9-deacetoxy-14,15-deepoxyxeniculin, as well as the one-step conversion to (−)-xeniafaraunol A.

Writing Strategy

☐ The Last Paragraph

总结工作

本文亮点

展望

- ✓ In conclusion, we have completed the first total syntheses of the xenicin natural products waixenicin A and 9-deacetoxy-14,15-deepoxyxeniculin.
- ✓ For the installation of the stereocenters at C11a and C4a, a highly diastereoselective conjugate addition/trapping sequence was employed. The characteristic 9-membered carbocycle of the natural products was constructed by a powerful intramolecular alkylation reaction.
- ✓ Current work in our laboratory focuses on late-stage diversification to access additional members of this natural product family as well as fully synthetic analogues for a broad bioactivity screening campaign against TRPM channels

Representative Examples

- ✓ Their synthesis has remained elusive for more than four decades. Here, we report the total synthesis of…(可以用来提出挑战)
- ✓ Inspiration came from the intramolecular Pd-catalyzed Tsuji−Trost reaction that…(灵感来自，用于提出设想)
- ✓ To this end, we first had to investigate the cleavage of dithiane to liberate the aldehyde function.(为此；至此，用于提出解决方法)

Acknowledgment

Thanks
for your attention