Spiroacetal Formation through Telescoped Cycloaddition and Carbon-hydrogen Bond Functionalization: Total Synthesis of Bistramide A

Reporter: Jie Wang
Checker: Yue Ji
Date: 2014/10/28

Floreancig, P. E. *et al. Angew. Chem. Int. Ed.* **2014**, *53,* 11075.

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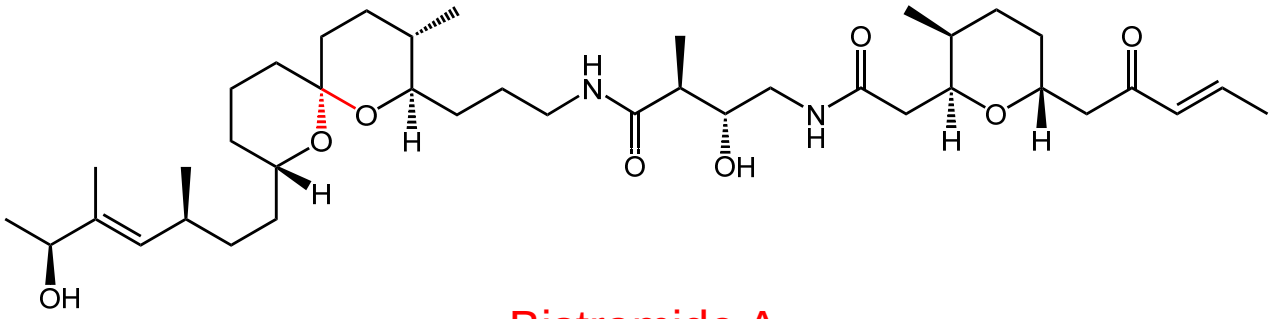
Introduction

海鞘

毒素机制：通过与肌动蛋白结合，阻止分裂过程中细胞的分离，从而阻断细胞的繁殖。

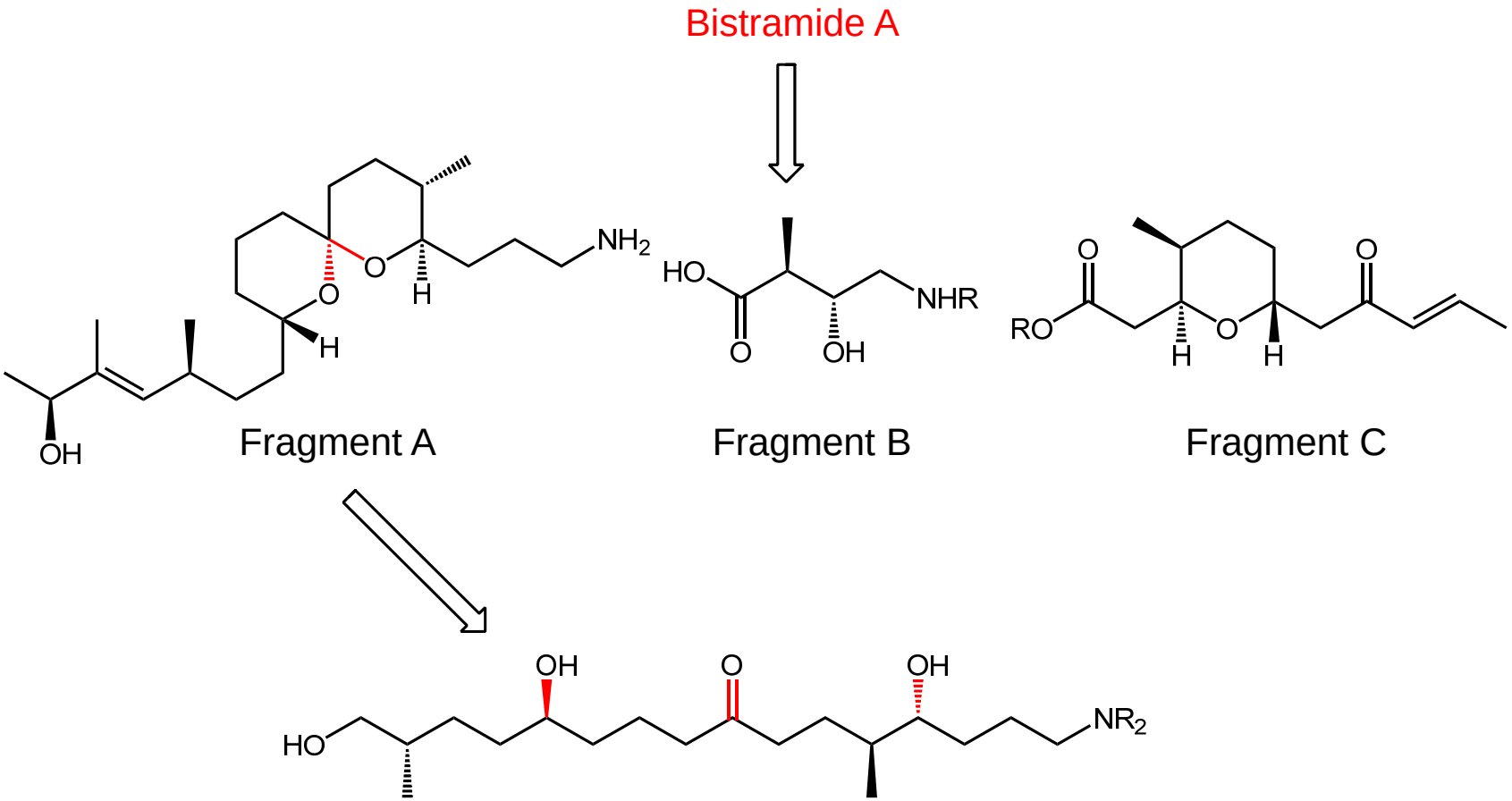
有效阻止癌细胞的分裂



Bistramide A

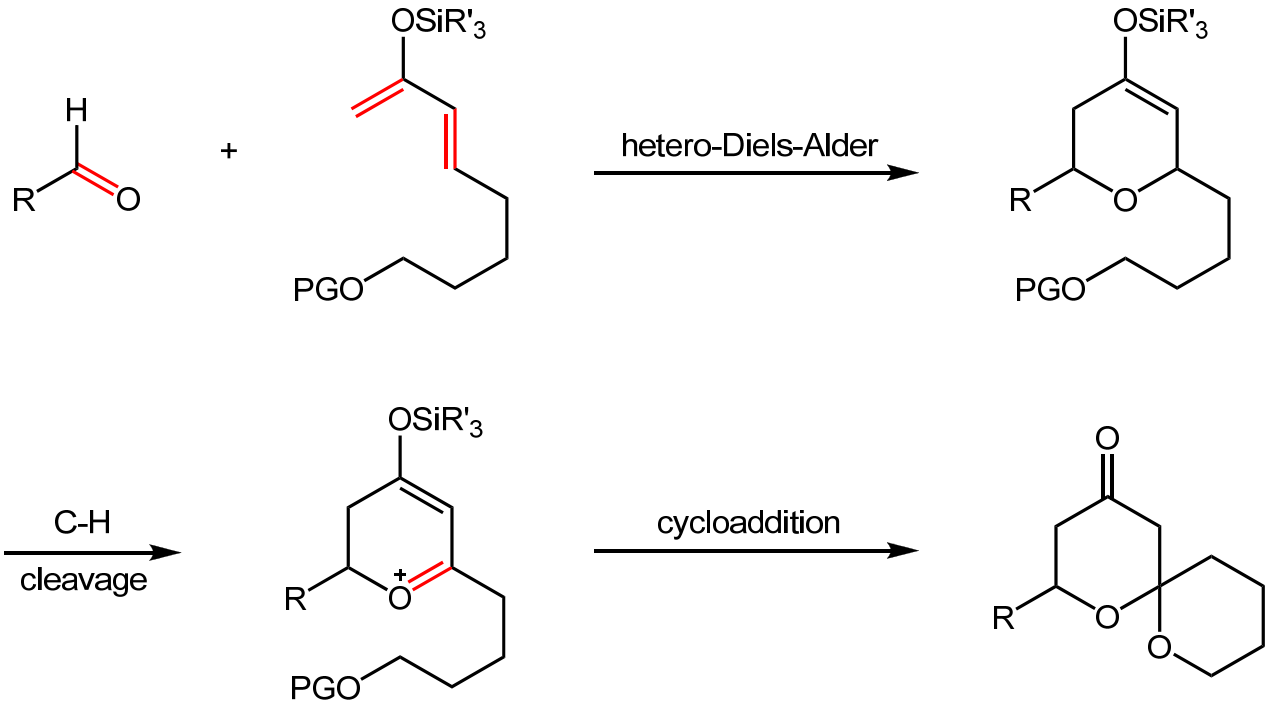
Verbist, J. F. *Tetrahedron* **1998**, *44*, 451.

Retrosynthetic Analysis of Bistramide A by Kozmin



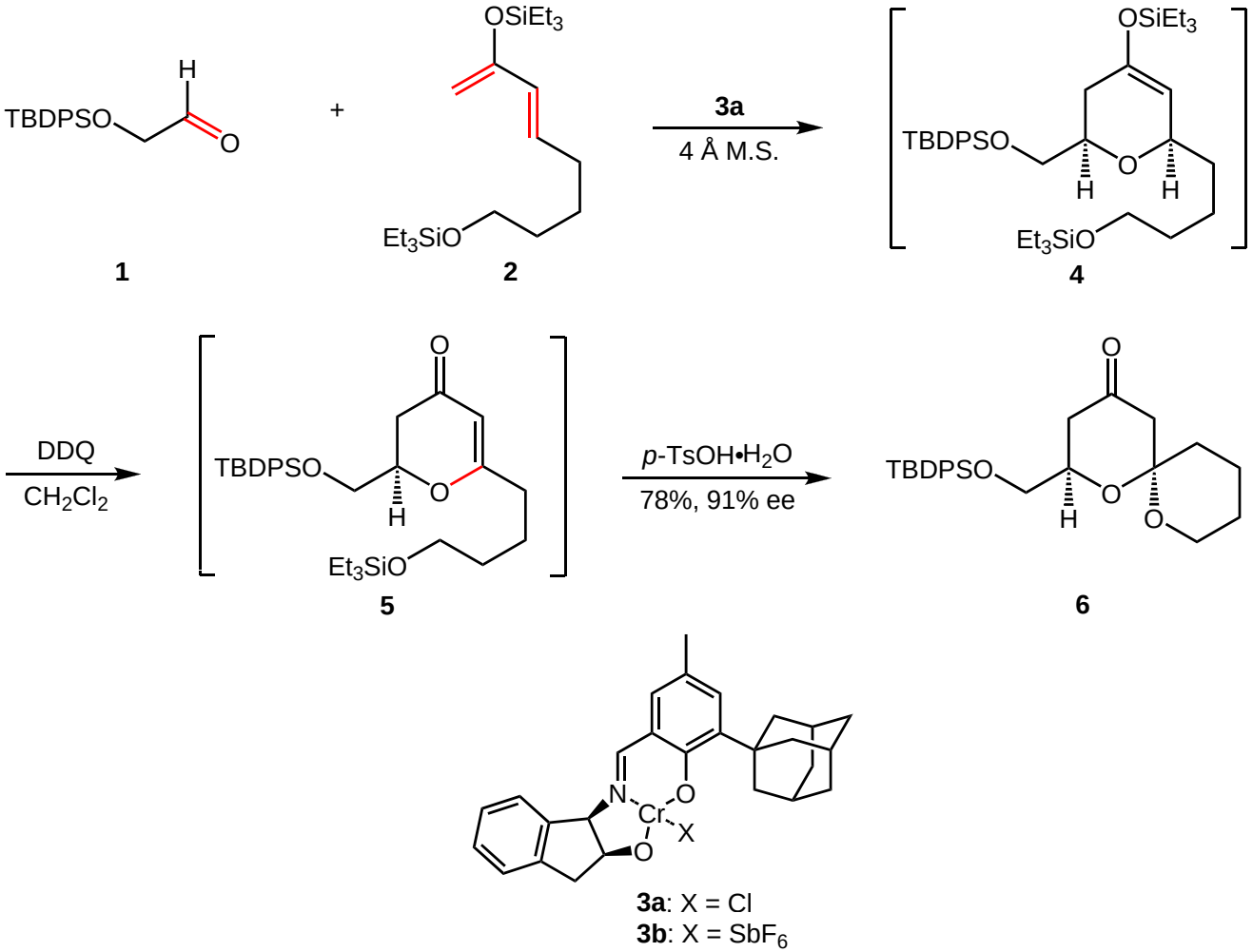
Kozmin, S. A. *et al*. *J. Am. Chem. Soc.* **2004**, *126*, 9546.

Total Synthesis of Bistramide A by Floreancig

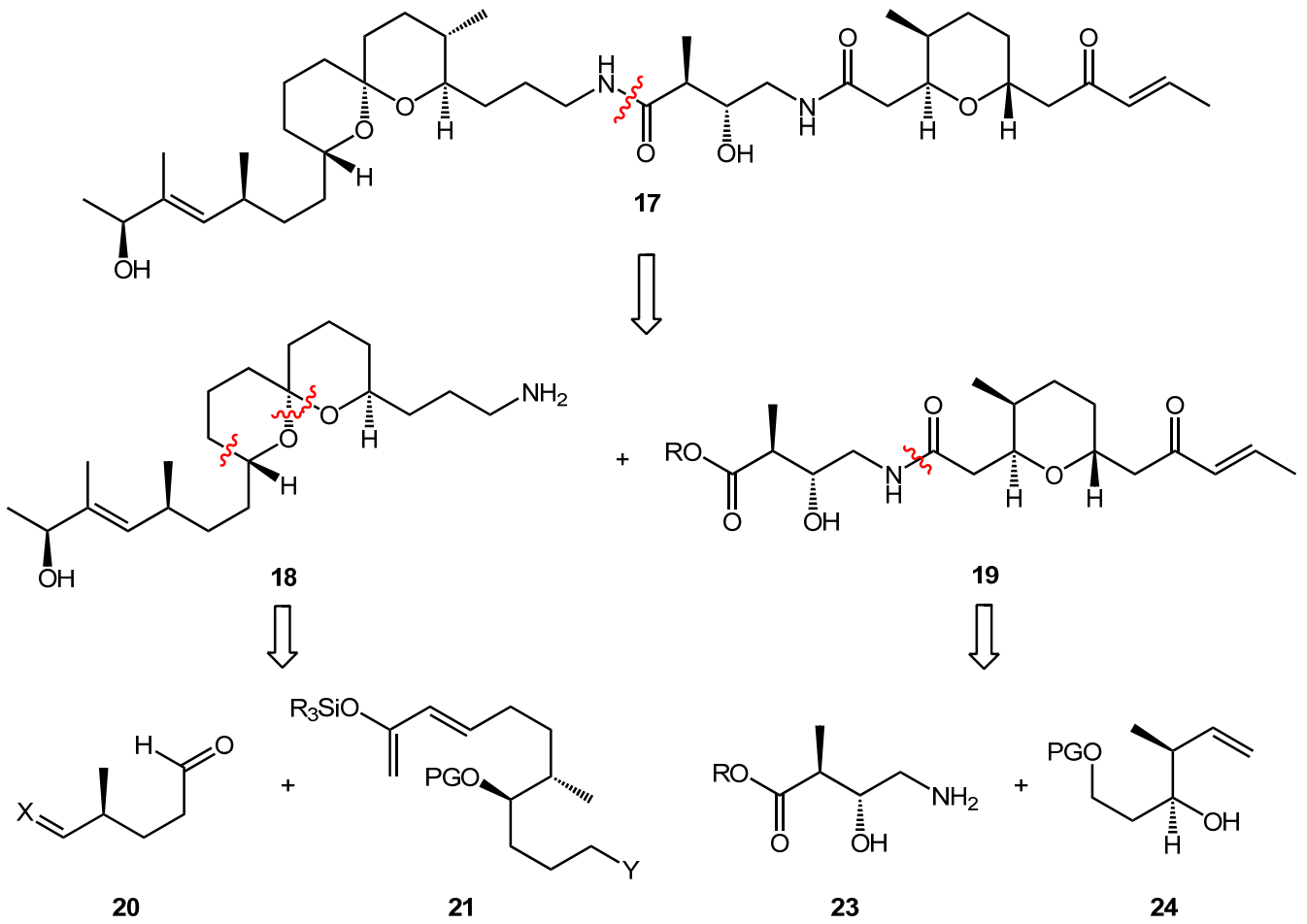


Floreancig, P. E. *et al. Angew. Chem. Int. Ed.* **2014**, *53,* 11075.

One-pot Spiroacetal Construction

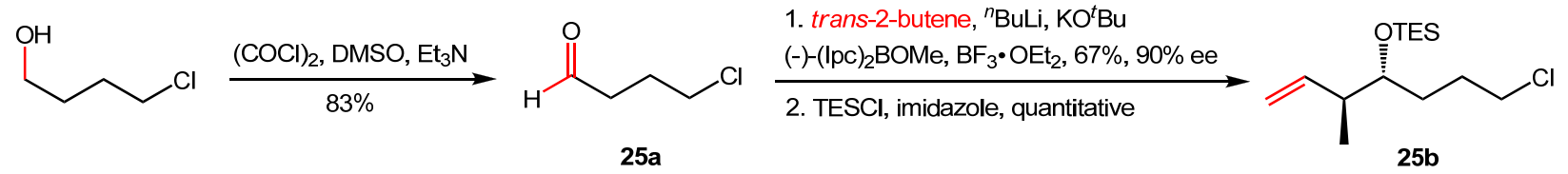


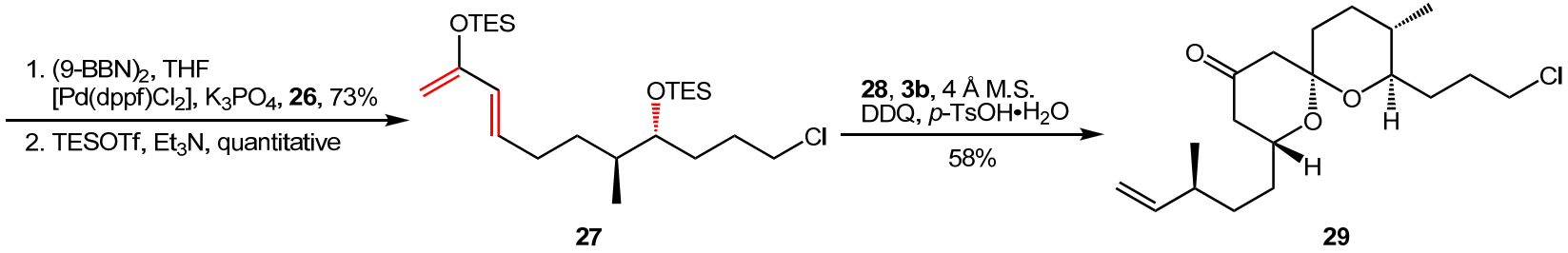
Retrosynthetic Analysis of Bistramide A by Floreancig

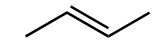


Synthesis of the Left-hand Fragment

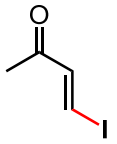
Brown Crotylation







trans-2-butene



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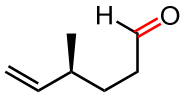

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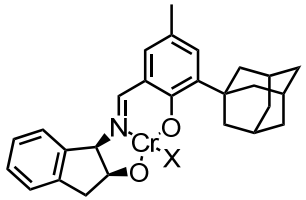
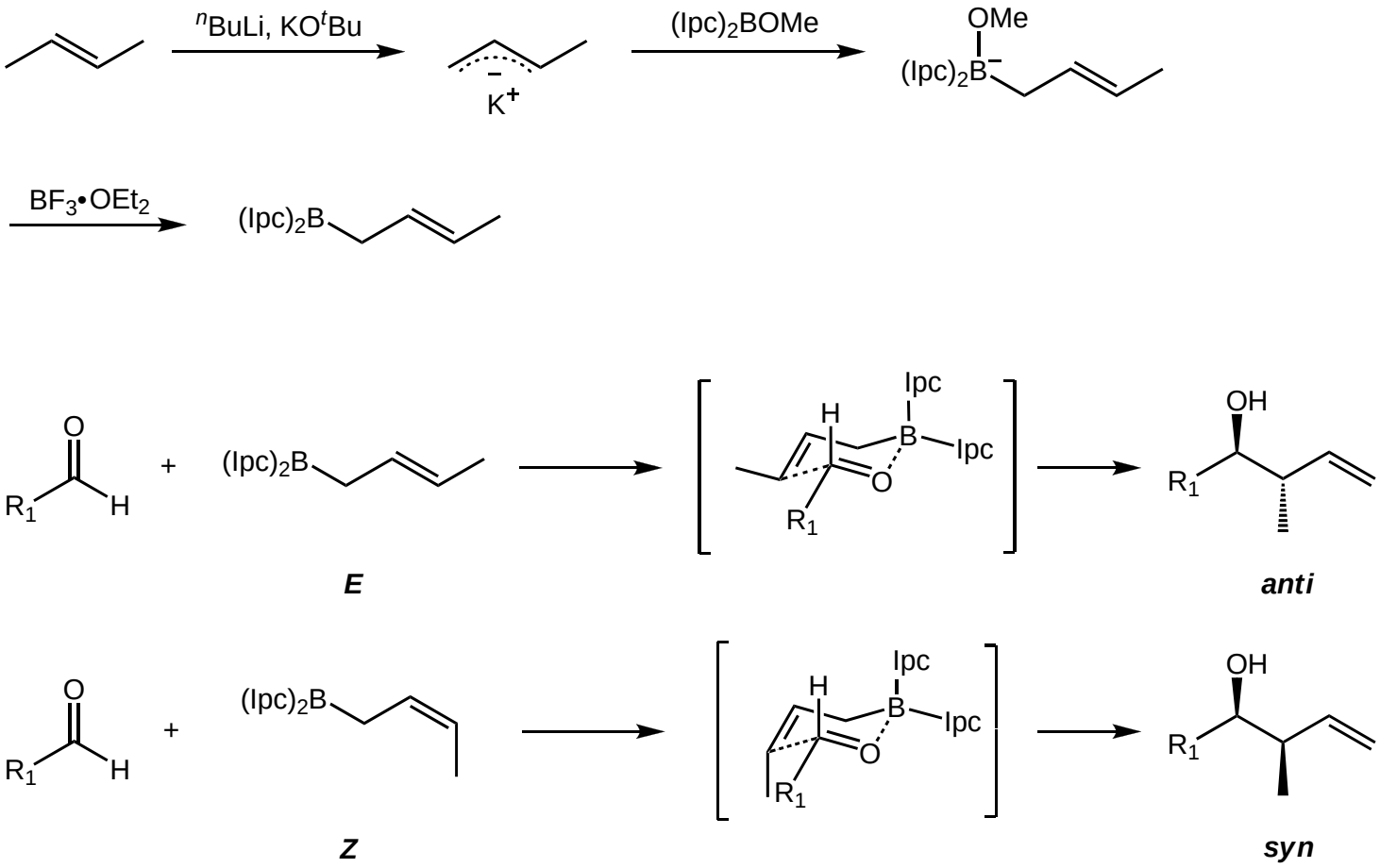


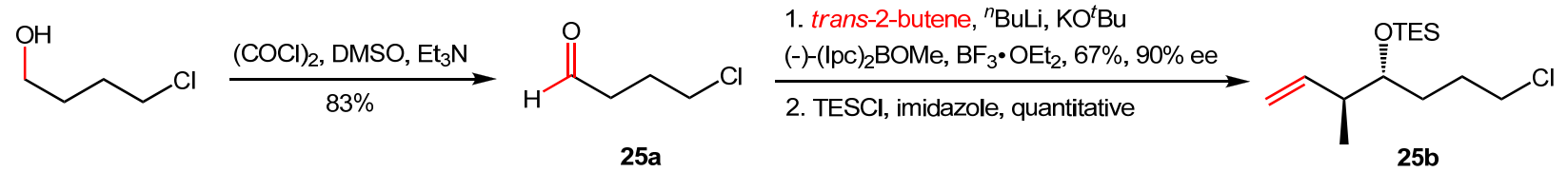
3b: X = SbF_6

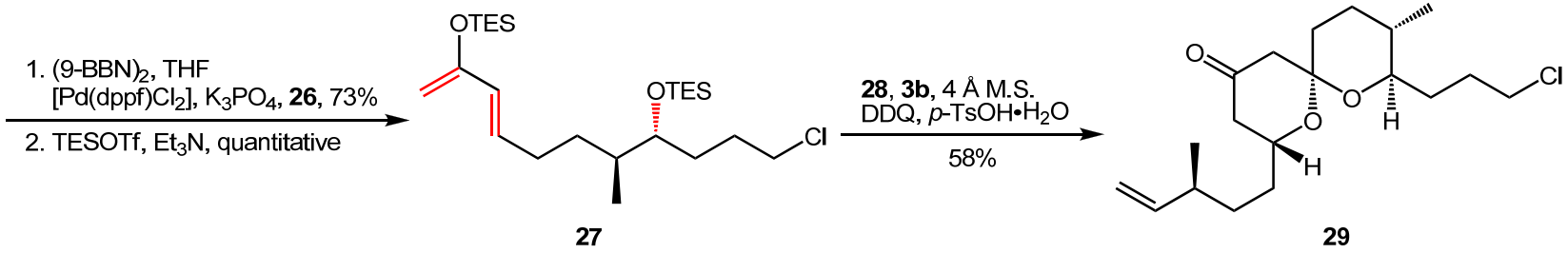
Brown Crotylation

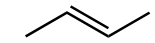


Brown H. C. *et al*. *J. Am. Chem. Soc*. **1986**, *108*, 293.

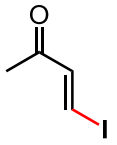
Synthesis of the Left-hand Fragment







trans-2-butene



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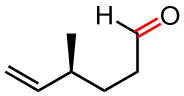

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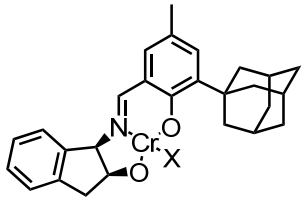

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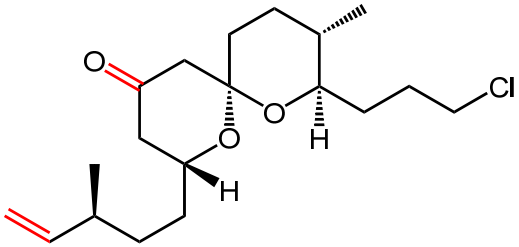

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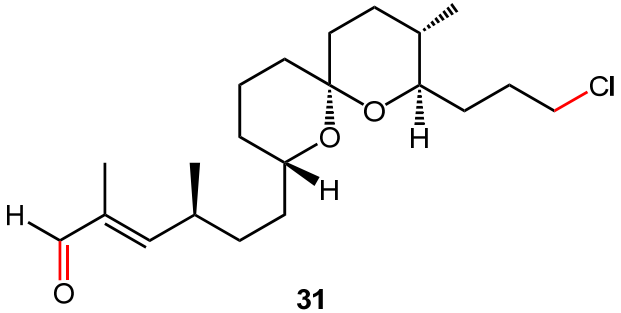
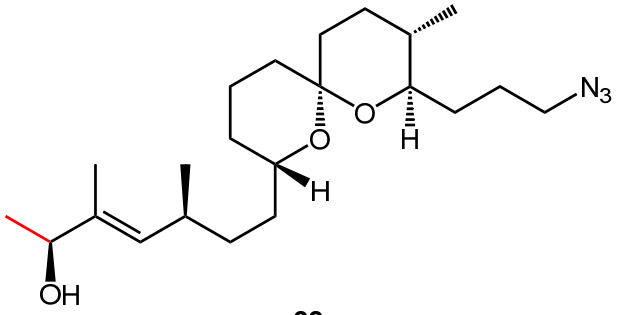
1. *p*-TsNHNH$_2$, MeOH
2. NaBH$_3$CN, MeOH, 54%
3. NaOAc, EtOH
4. mathacrolein, **30**, 68%

Olefin Metathesis reaction



31

1. Me_2Zn, **32**, 86%
2. NaN_3, quantitative



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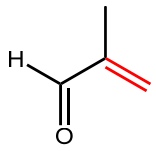
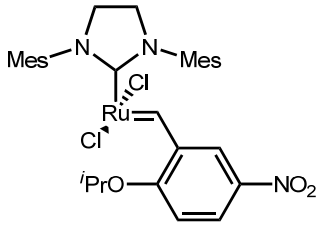


mathacrolein



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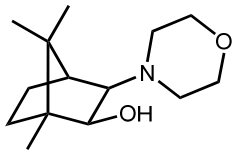

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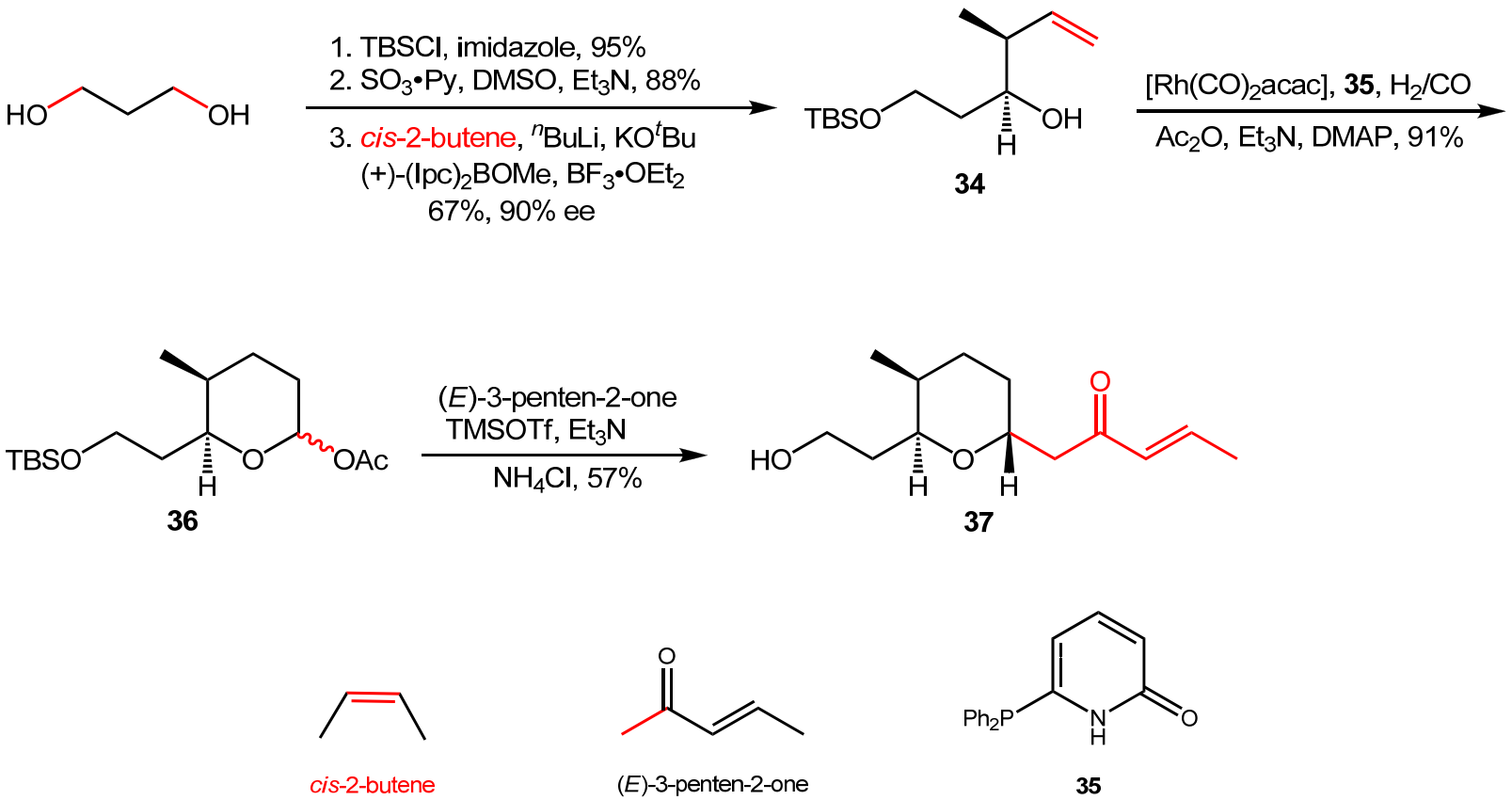
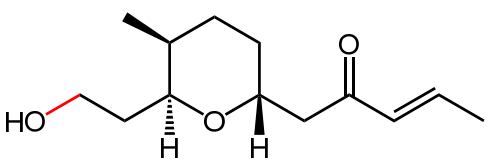
Synthesis of the Right-hand Fragment



Synthesis of the Right-hand Fragment



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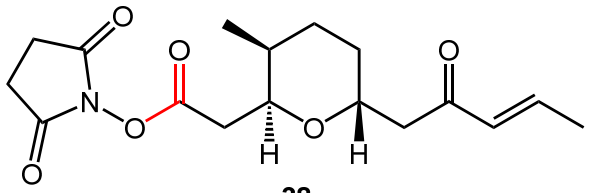
1. H_5IO_6, CrO_3, CH_3CN, H_2O

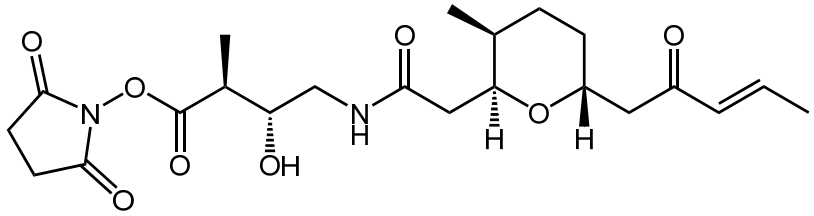
2. *N*-hydroxysuccinimide, DCC, 81%



38

1. **39**, $^{i}Pr_2NEt$, DMF

2. *N*-hydroxysuccinimide, DCC, 50%



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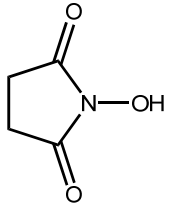
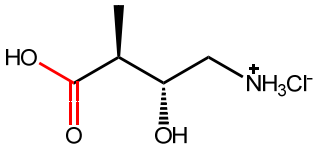


***N*-hydroxysuccinimide**



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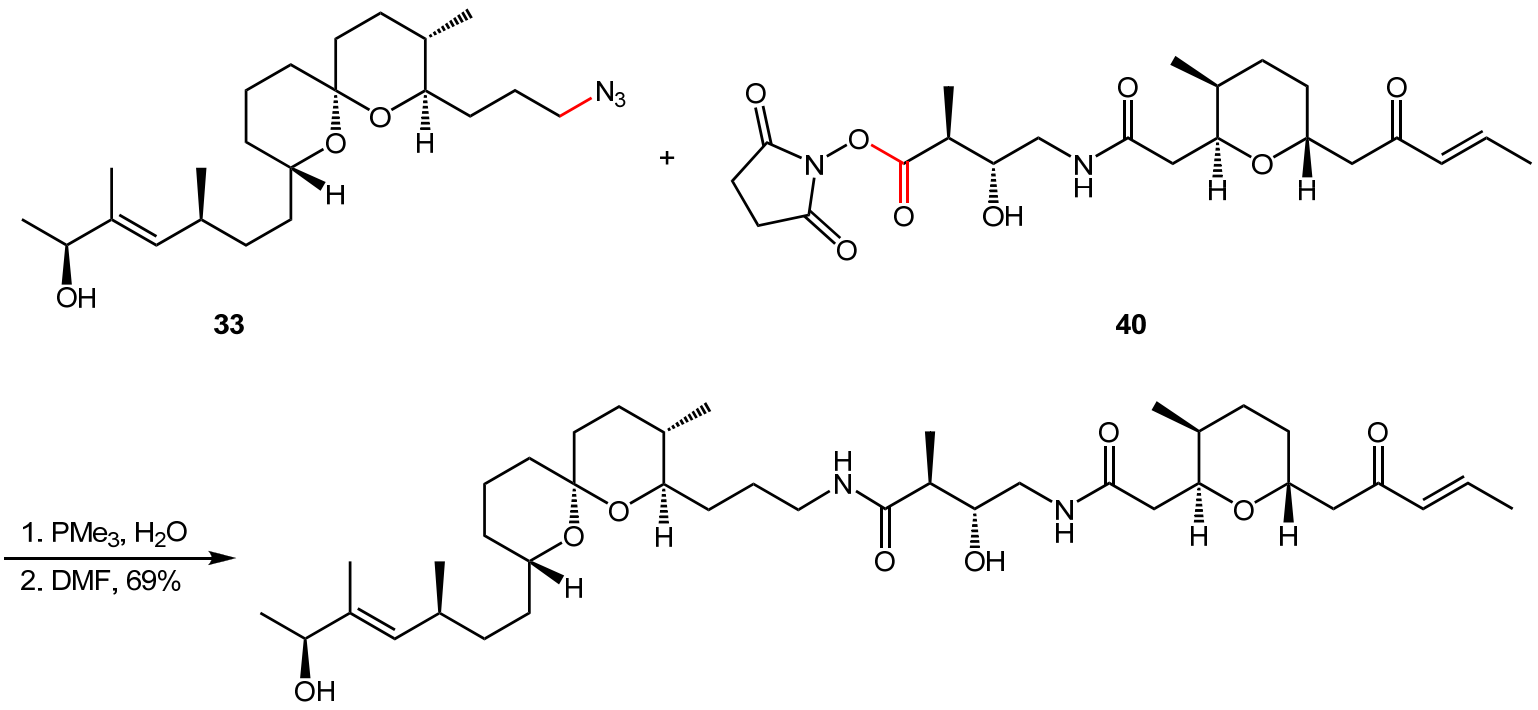
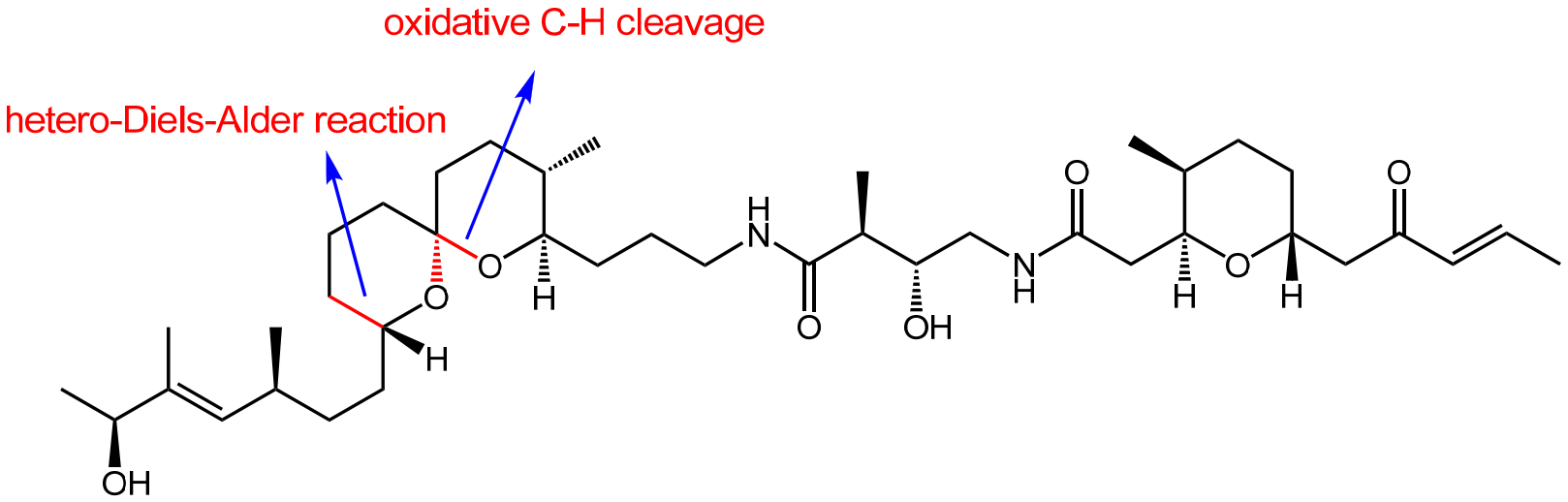
Completion of the Synthesis



Bistramide A

Summary



14 steps linear sequence, 4.9% yield

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Transformations that generate multiple product-relevant bonds facilitate complex molecule synthesis. Intermolecular cycloaddition reactions such as the hetero-Diels–Alder reaction are ideally suited for this objective. Oxidative carbon–hydrogen bond functionalization also introduces product-relevant bonds from structurally simple precursors. This manuscript describes a telescoped sequence comprising an asymmetric hetero-Diels–Alder reaction and oxidative carbon–hydrogen bond functionalization to access spiro-acetals. These units are components of numerous biologically active structures and have inspired multiple synthetic approaches. The mild and convergent protocol described herein provides a step-economical approach to the construction of these structures. The applicability of the sequence to complex molecule synthesis is demonstrated through the total synthesis of the cytotoxin bistramide A.

We have demonstrated that the benefits of fragment coupling asymmetric cycloaddition reactions can be merged with the complexity-increasing capabilities of oxidative carbon–hydrogen bond cleavage for a convergent synthesis of spiroacetals. The substrates are easily prepared, functional group tolerance is high, and stereocontrol is excellent, thus indicating that this protocol will be applicable to natural product synthesis. The rapid complexity that this sequence provides was exploited in the shortest reported synthesis of the actin-binding cytotoxin bistramide A.