Jingbo Xiao
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A Diels-Alder Macrocyclization Enables an Efficient Asymmetric Synthesis of the Antibacterial Natural Product Abyssomicin C

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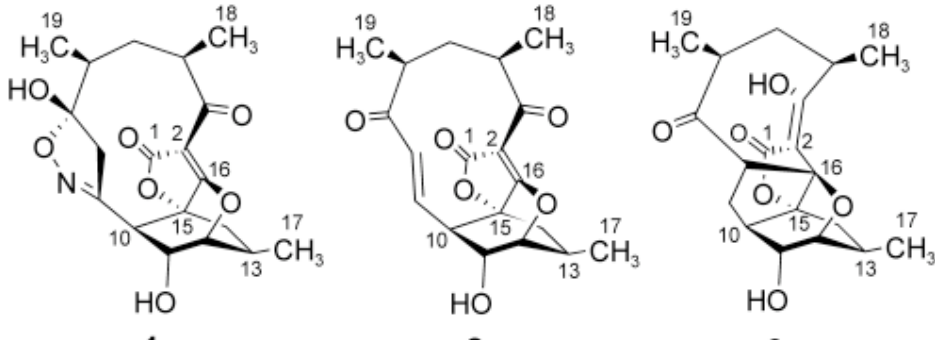
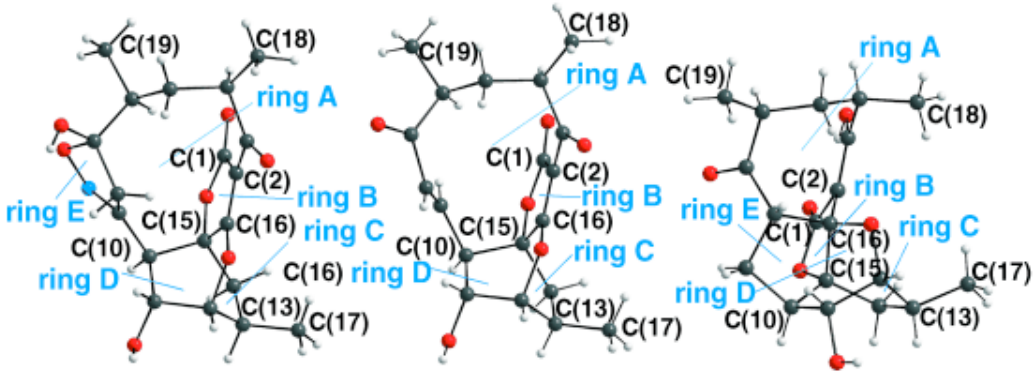
Angew. Chem., Int. Ed. **2005, *44*, 6533-6537.**

Isolation



1 **Abyssomicin B** **2** **Abyssomicin C** **3** **Abyssomicin D**



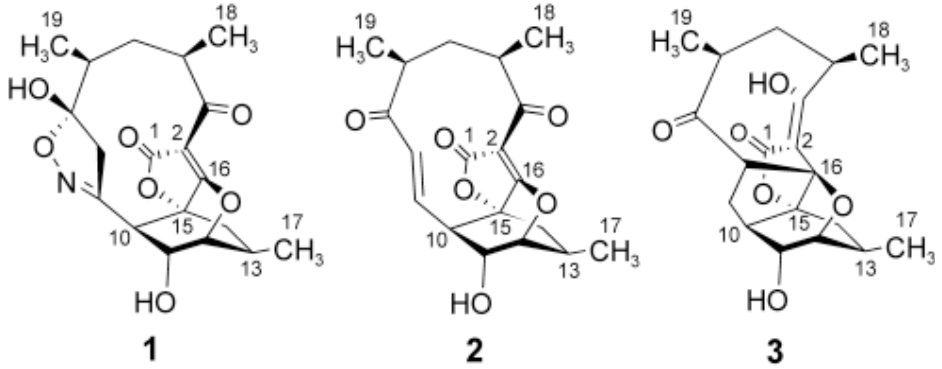
1 **2** **3**

Large number of ring systems, quarternary canter, Tetron moiety and stereocenters.

Abyssomicin B-D were isolated from a sediment sample collected in the Japanese sea at depth of 289 m. The structures were confirmed by NMR and X-ray.

***Sussmuth, R. D. et al. Angew. Chem., Int. Ed.* 2004, *43*, 2574.**

Biological Activity



1 **2** **3**

Abyssomicin B	**Abyssomicin C**	**Abyssomicin D**
No activity	**activity**	**No activity**

Hydroxylamine Michael addition **Hydride Michael addition**

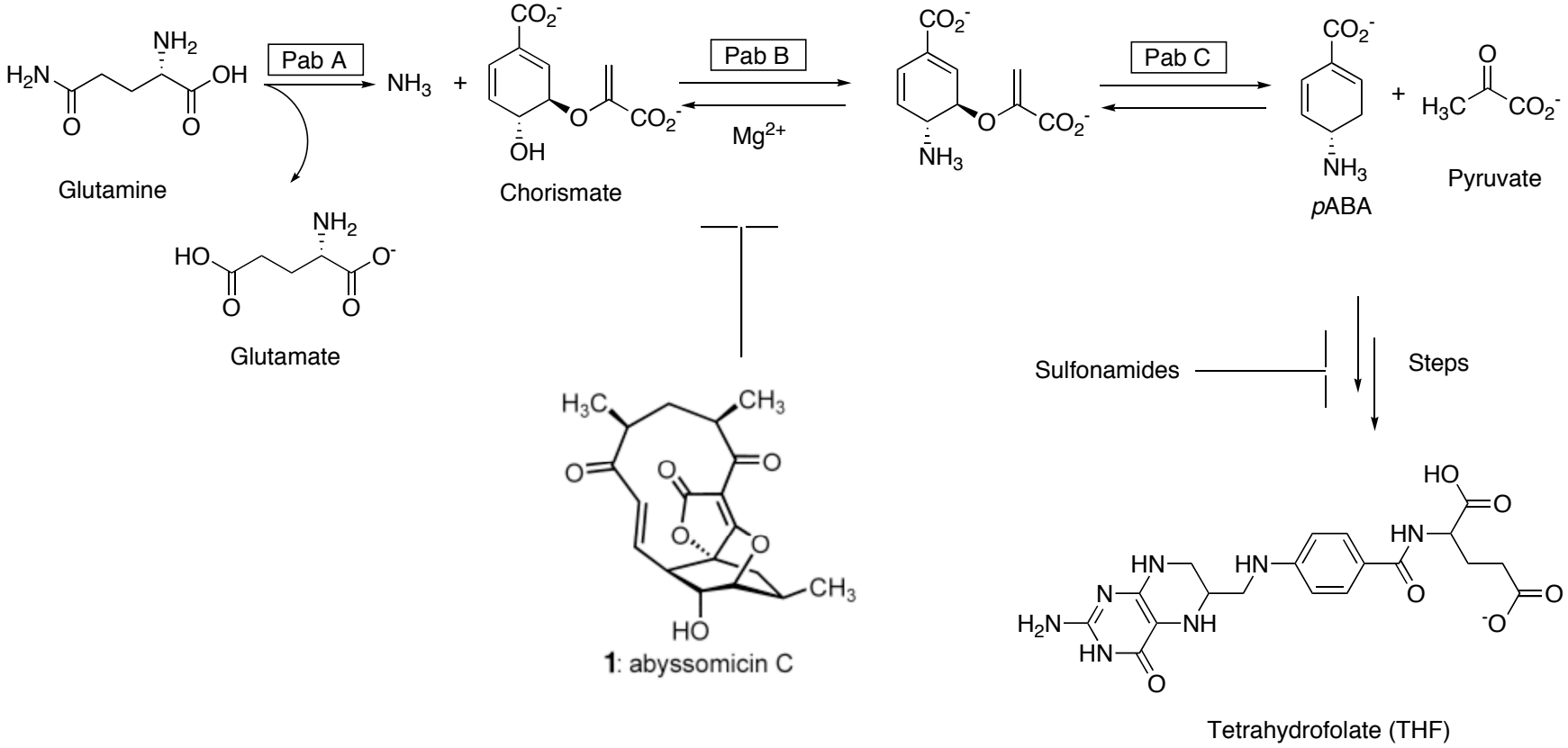
1. **Abyssomicin C showed antibiotic activity against Gram-positive bacteria ~ 4 - 13 μg/mL.**

2. **Inhibition of *p*-aminobenzoate (*p*ABA) biosynthesis, which is found in many microorganisms but not in human.**

3. **Abyssomicin C is the first known substance derived from a bacterial source that inhibit the biosynthesis of *p*ABA.**

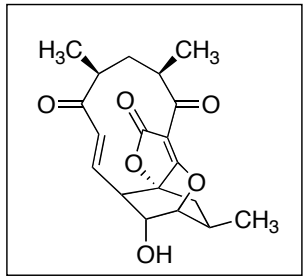
***Sussmuth, R. D. et al. Angew. Chem., Int. Ed.* 2004, *43*, 2574.**

Possible Inhibition Path Way

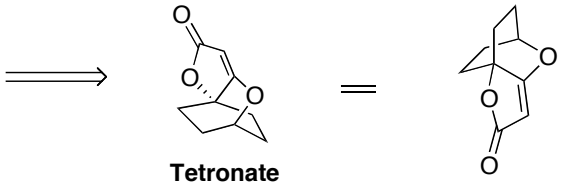


Anderson, K. S. et al. J. Am. Chem. Soc. **1991**, *113*, **3198.**

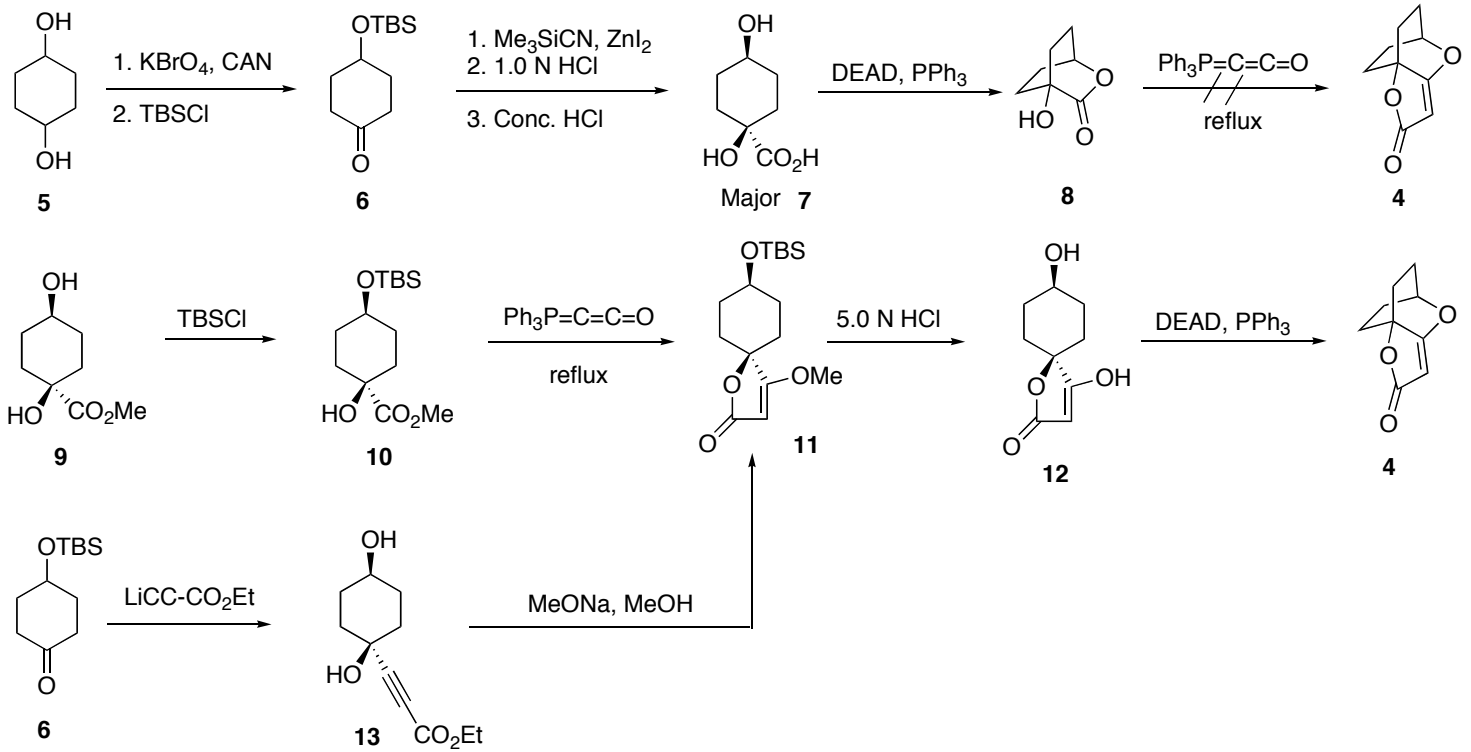
Model Synthesis of Abyssomicin C Core Structure I



Abyssomicin C

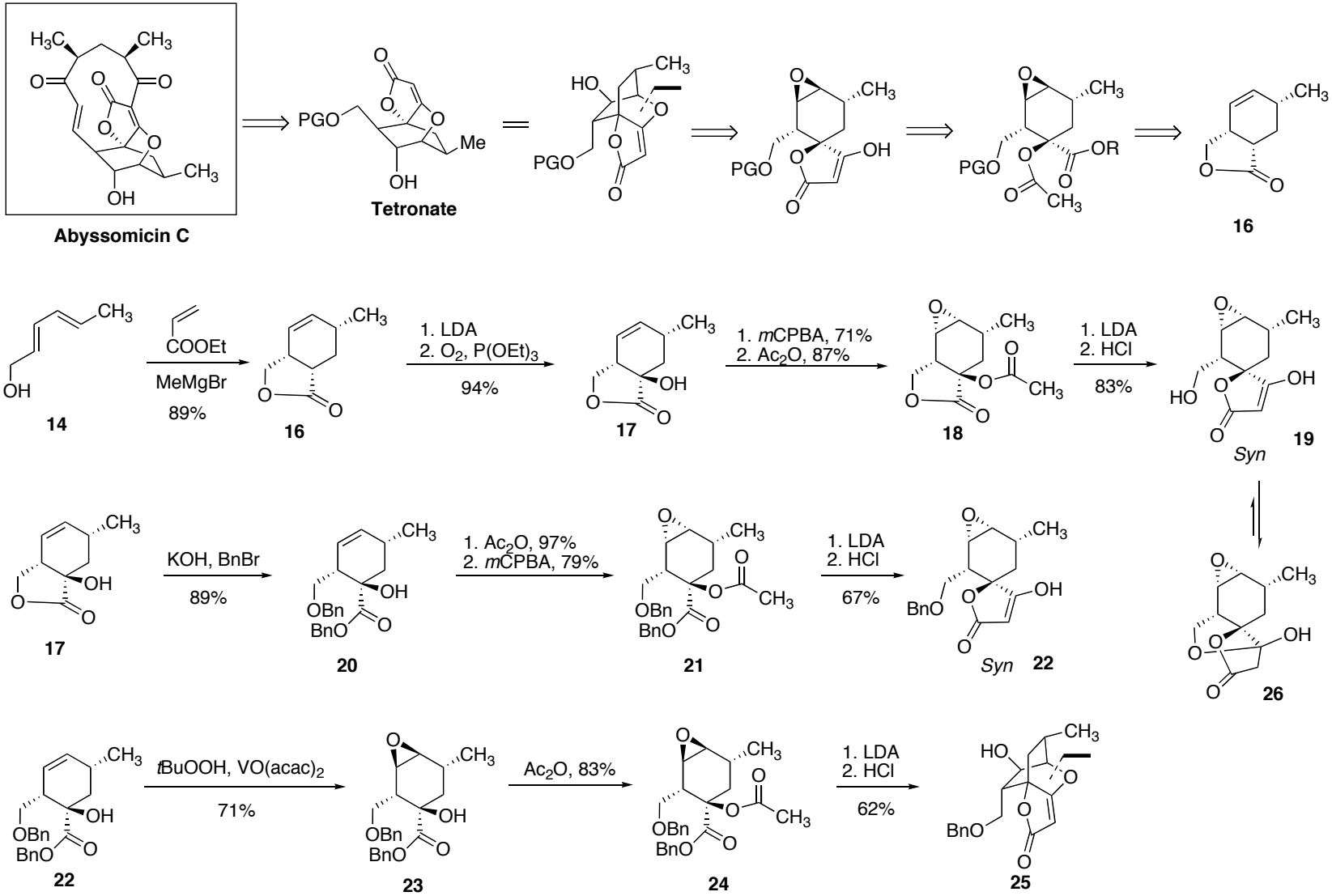


Tetronate **4**



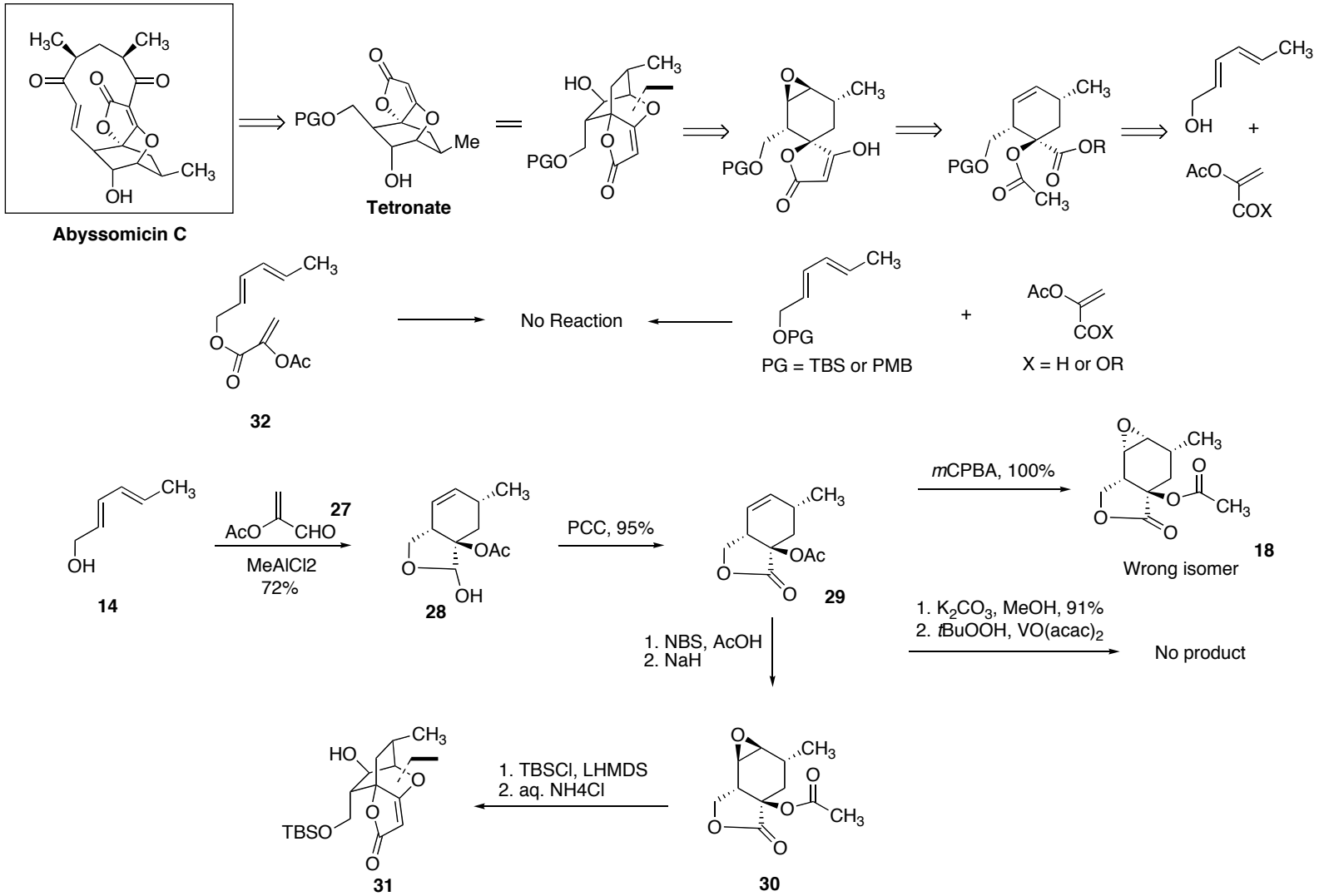
***Maier, M. E. et al. Synlett.* 2005, 314.**

Model Synthesis of Abyssomicin C Core Structure II



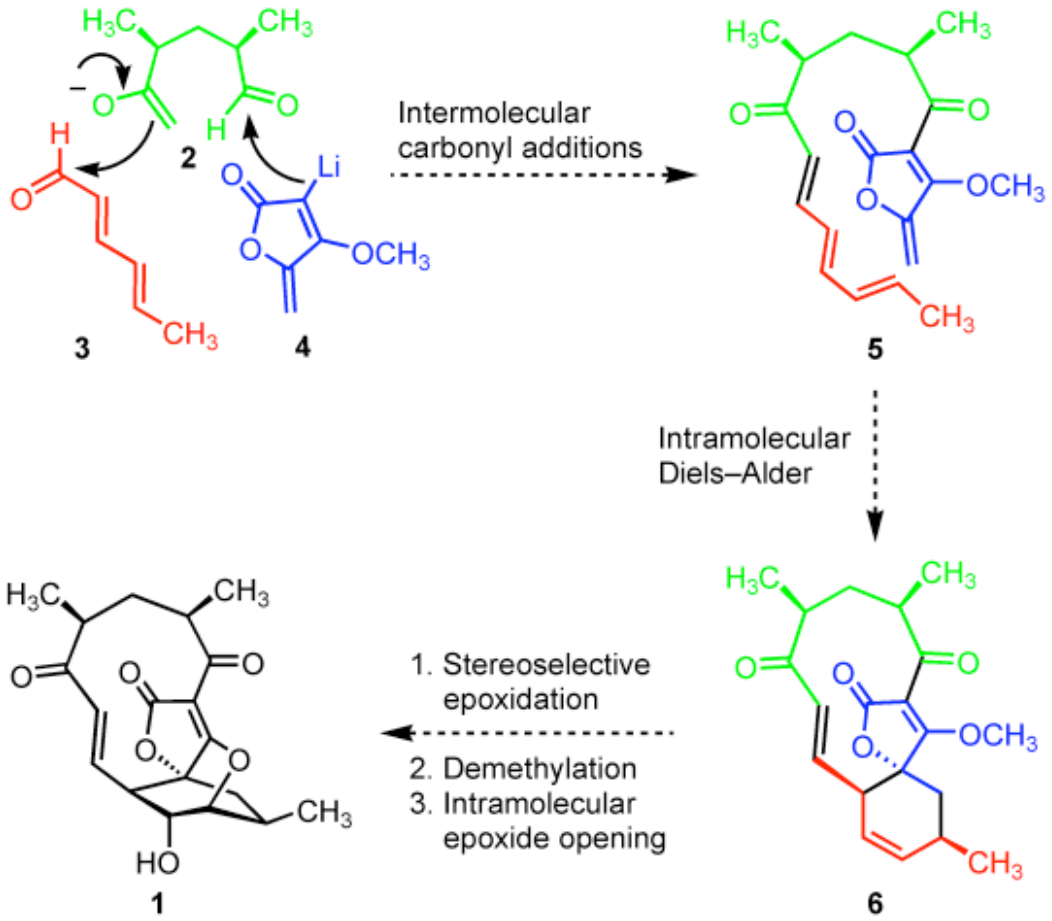
***Maier, M. E. et al. Org. Lett.* 2005, *7*, 3089.**

Model Synthesis of Abyssomicin C Core Structure III



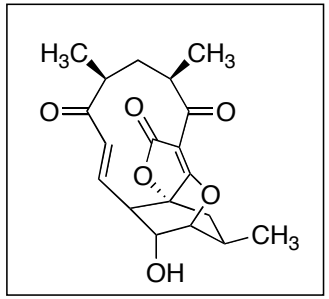
***Georgiadis, D. et al. Org. Lett.* 2005, *7*, 4515.**

Retrosynthesis of Abyssomicin C

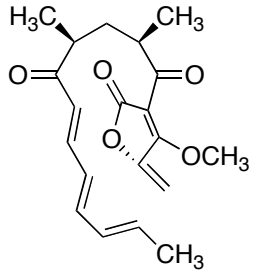


***Sorensen, E. J. et al. Angew. Chem., Int. Ed.* 2005, *44*, 6533.**

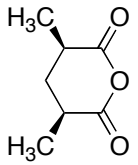
Synthesis of the Intramolecular DA Reaction Substrate



Abyssomicin C

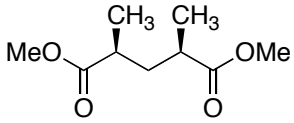


34



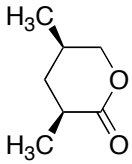
33

1. MeOH, reflux
2. MeOH, H+, 87%



35

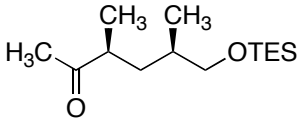
1. a-chymotrypsin, pH 7.8, 96%
2. $LiBH_4$, then HCl, H_2O, 60%



36

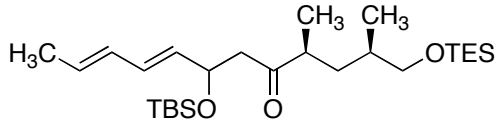
93% ee

1. MeLi
2. TESCl, imid., 79%



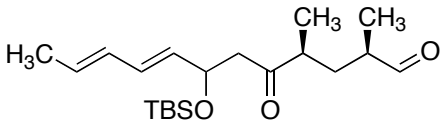
37

1. LDA, then 2,4-hexadienal, 94%
2. TBSOTf, 2,6-lutidine, 85%

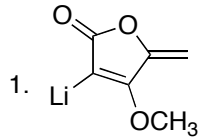


38

Swern Oxid., 60-70%



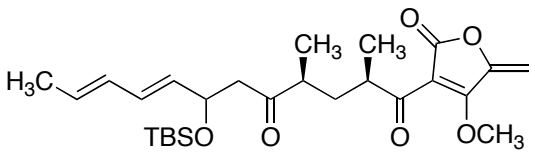
39



40

1. Li
2. tol, 35-55%

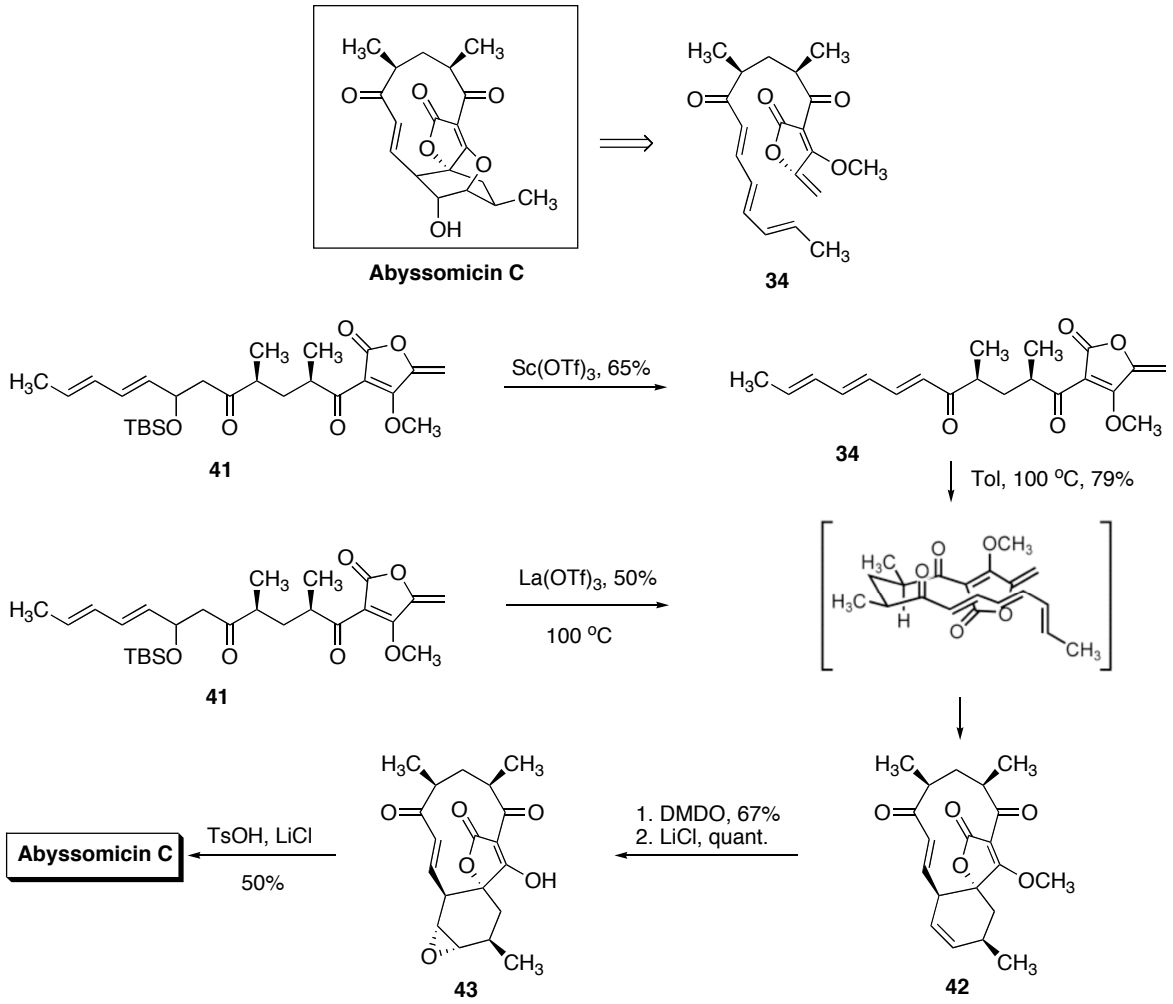
2. Dess-Martin, 84%



41

***Sorensen, E. J. et al. Angew. Chem., Int. Ed.* 2005, *44*, 6533.**

Asymmetric Total Synthesis of Abyssomicin C

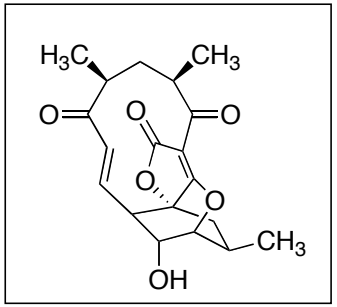


***Sorensen, E. J. et al. Angew. Chem., Int. Ed.* 2005, *44*, 6533.**

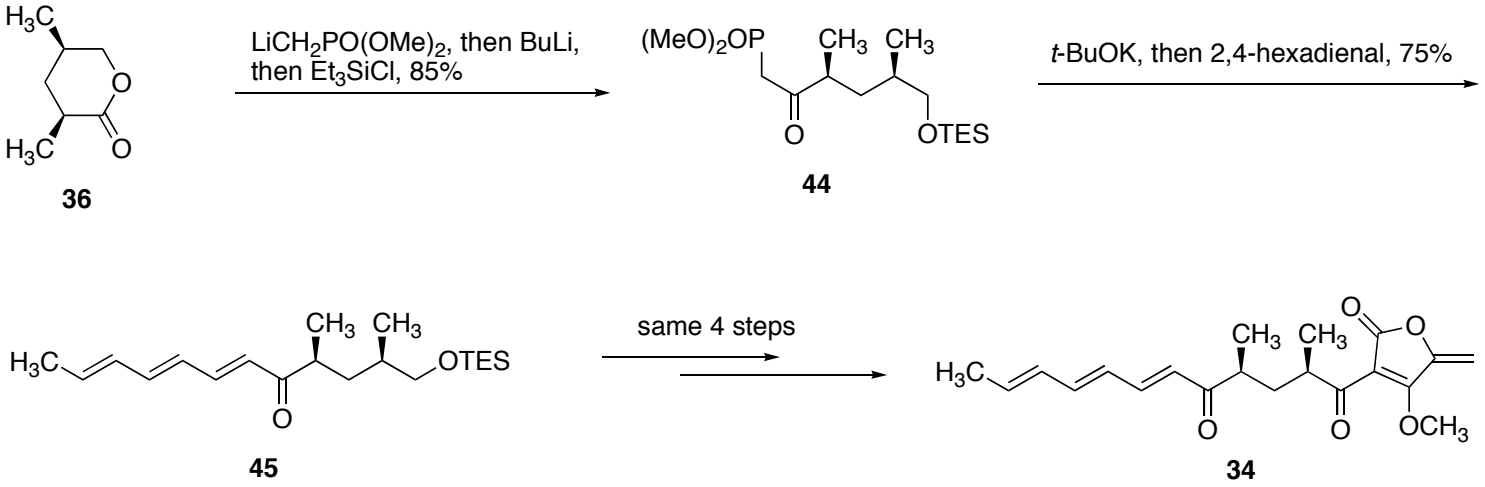
In summary, a concise enantioselective synthesis of Abyssomicin C was achieved in 15 steps from the known compound by a reaction sequence that features a highly diastereo-selective Diels-Alder macrocyclization.

It can procure significant amounts of the natural abyssomicin C by this route, which should facilitate the investigation of the interesting biological properties.

Asymmetric Total Synthesis of Abyssomicin C



Abyssomicin C



***Snider, B. B. et al. Org. Lett.* 2005, *7*, *ASAP*.**