Gold(I) as an Artificial Cyclase: Short Stereodivergent Syntheses of (-)-Epiglobulol and (-)-4α,7α- and (-)-4β, 7α-Aromadendranediols

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Checker : Yue Ji

Date: 2014/10/21

Echavarren, A. M. *et al. Angew. Chem. Int. Ed*. **2014**, *53*, 4896

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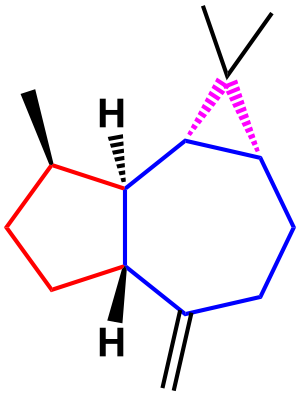
1. Introduction

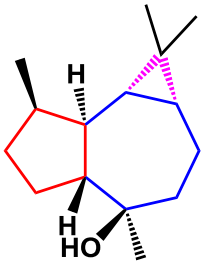


(+)-Aromadendrene

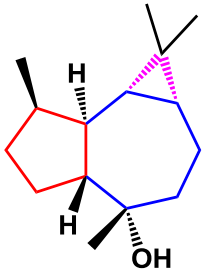
Eucalyptus (桉树)

- 1901年第一次从桉树叶中分离得到
- 1953年结构得到确认
- 一个五元环并一个七元环并一个三元环，具有五个手性中心

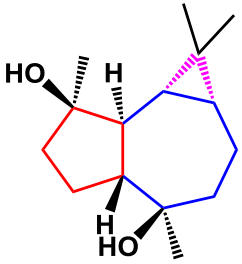
1. Introduction



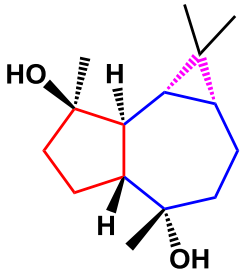
(-)-Globulol



(-)-Epiglobulol



(-)-4α,7α-Aromadendranediol



(-)-4β,7α-Aromadendranediol

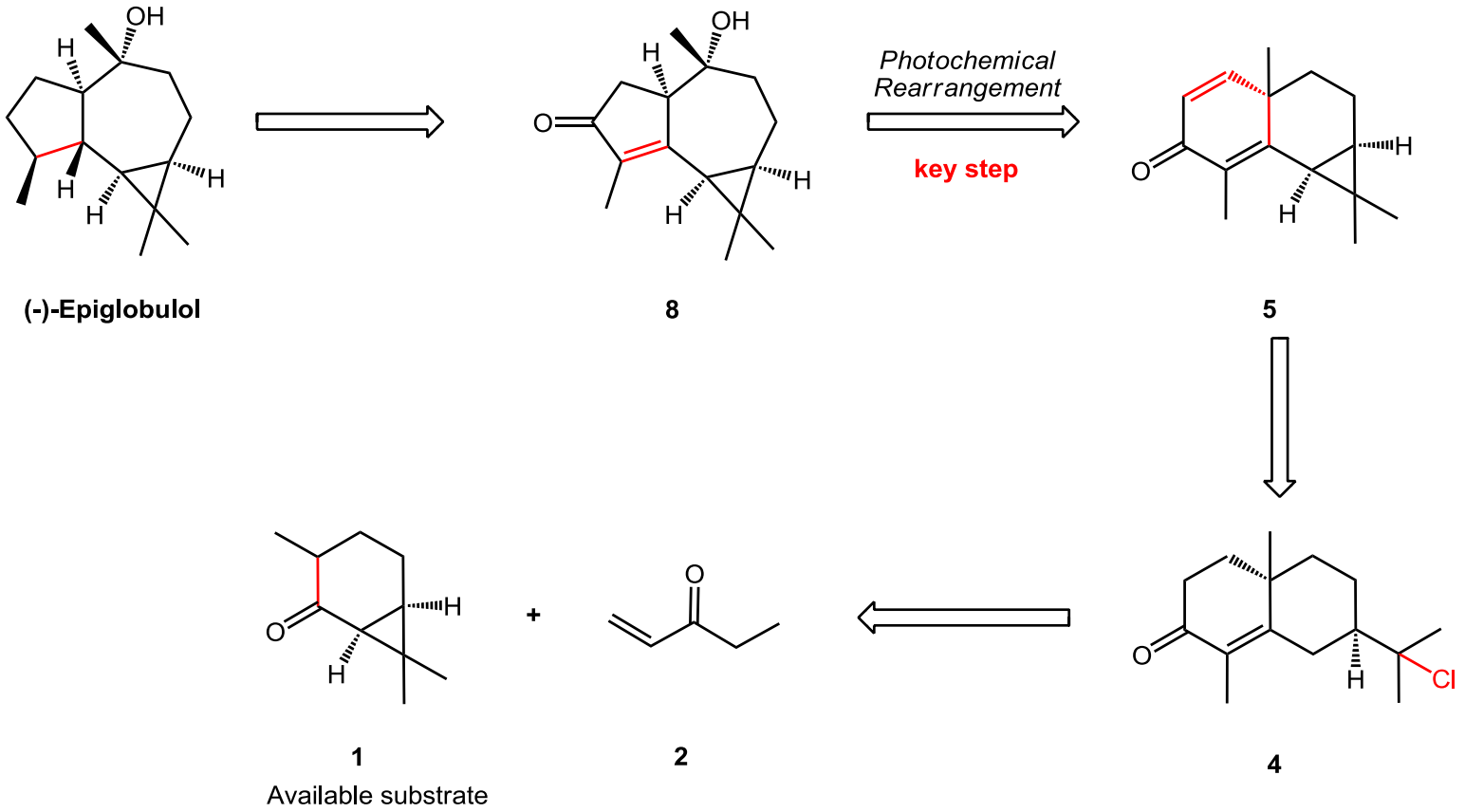
具有抗细菌，抗真菌等生理活性

Koepple. H. *et al*. *J. Agric. Food Chem.* **1983**, *31*, 892

Groot. A. *et al*. *Prog. Chem. Org. Nat. Prod.* **1995**, *64*, 149

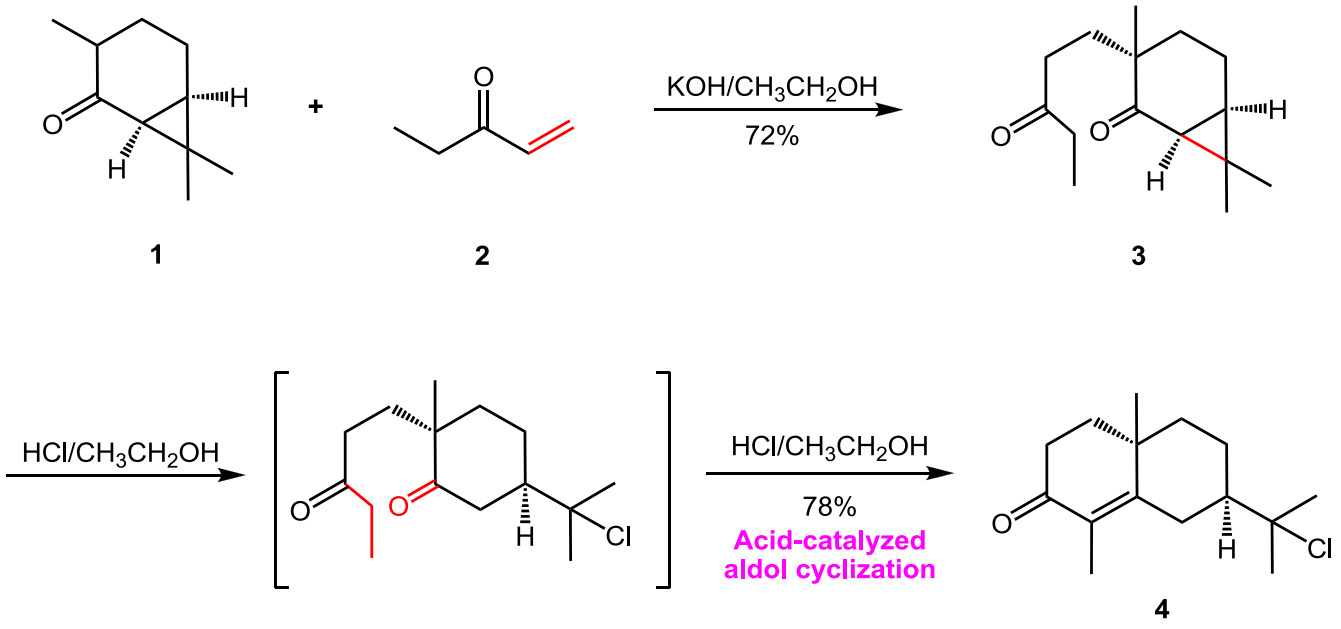
2. First total synthesis by Gupton

Retrosynthetic analysis as follow:



Gupton III J. T. *et al*. *J. Org. Chem*. **1974**, *39*, 2654

2. First total synthesis by Gupton



Gupton III J. T. *et al*. *J. Org. Chem*. **1974**, *39*, 2654

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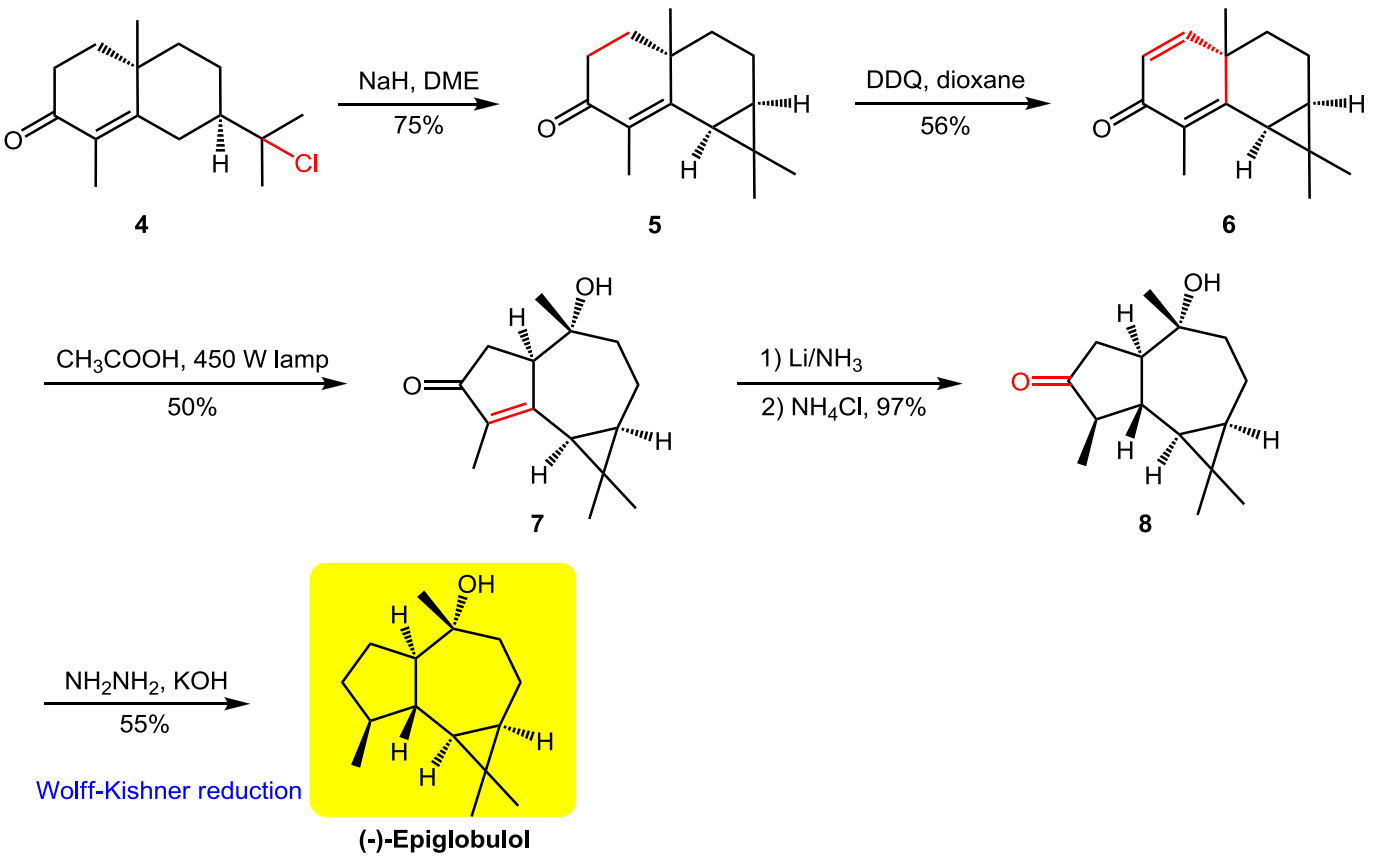
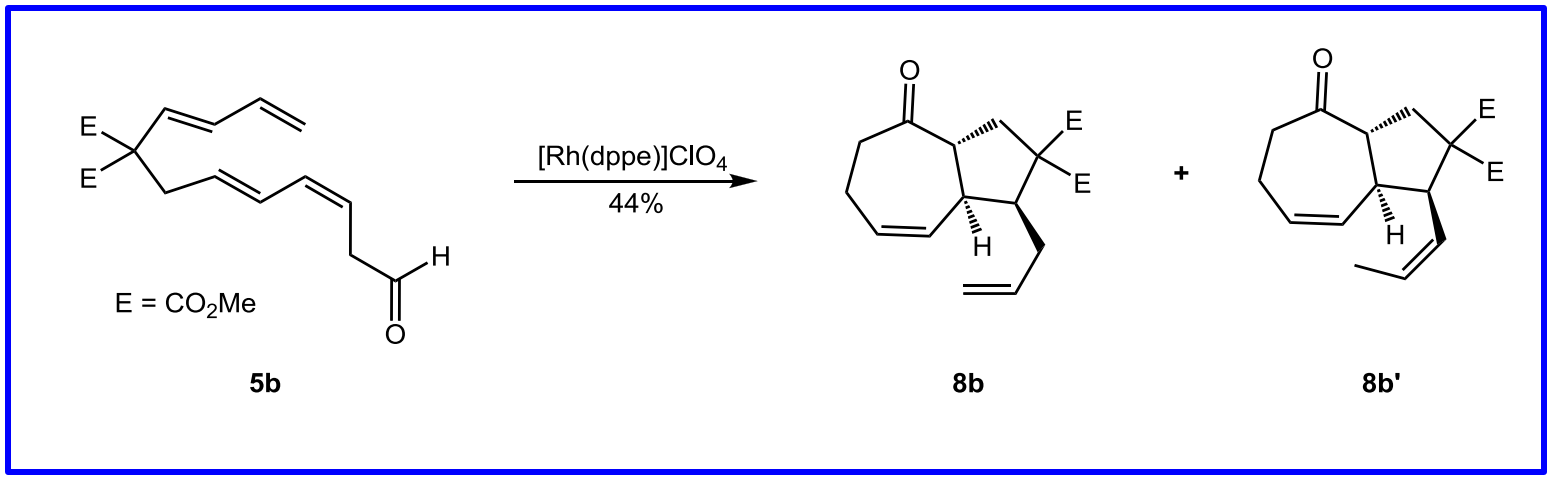


Gupton III J. T. *et al*. *J. Org. Chem*. **1975**, *40*, 809

3. Total synthesis by Sato

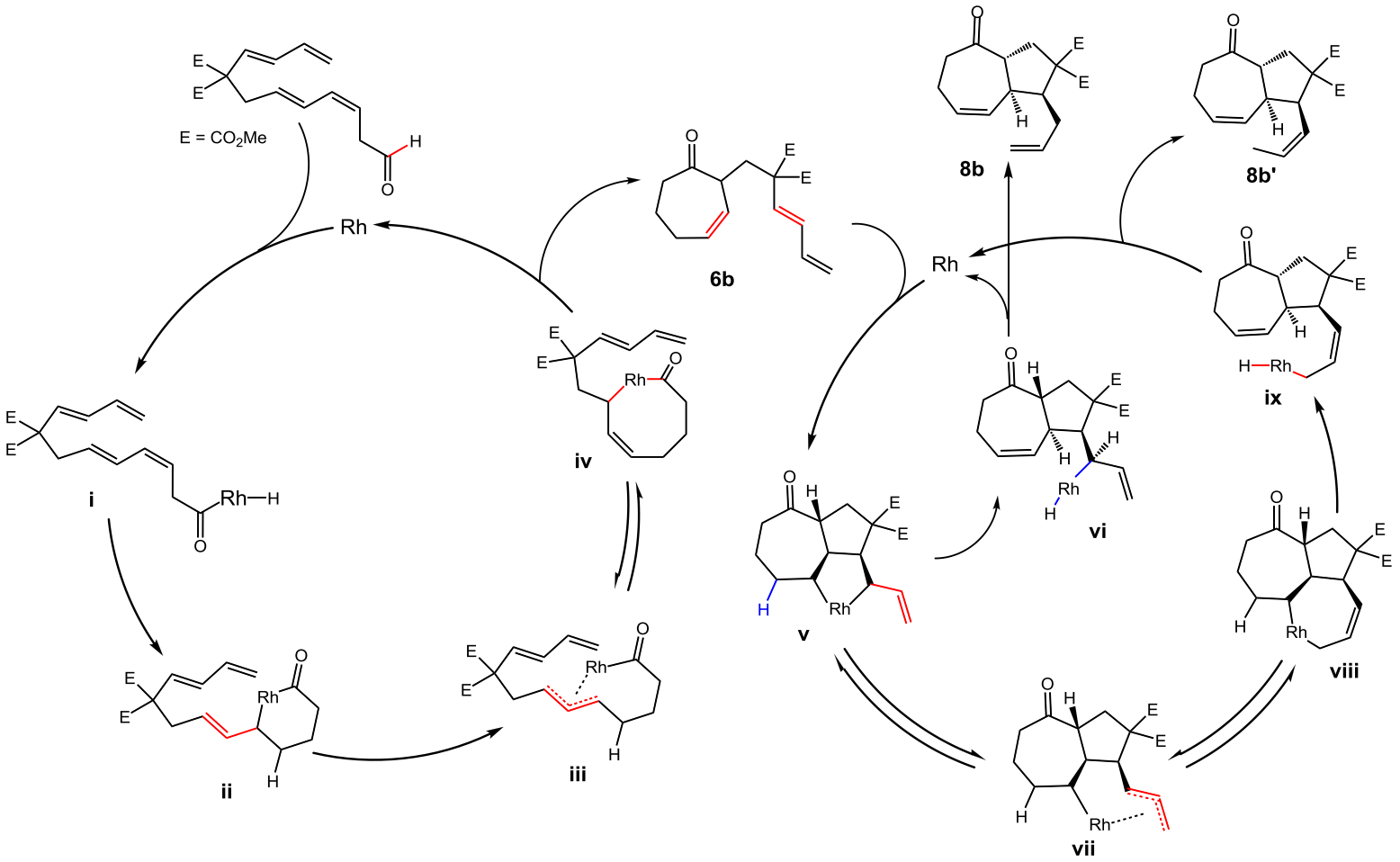
Rh(I)-catalyzed hydroacylation/cycloisomerization cascade



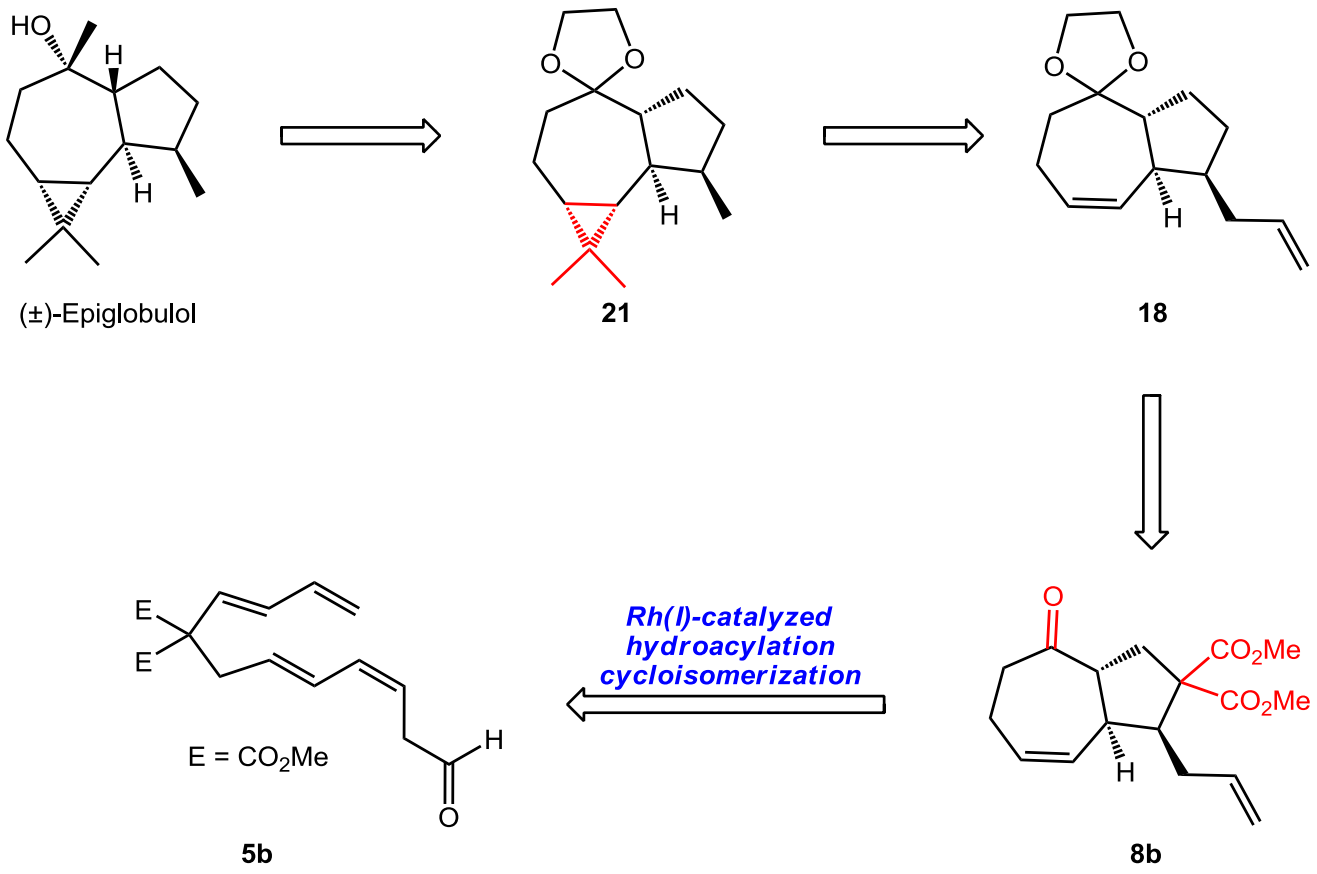
5b **8b** **8b'**

Sato, Y. *et al. Tetrahedron Lett.* **2006**, *47*, 5617

A possible mechanism of this reaction

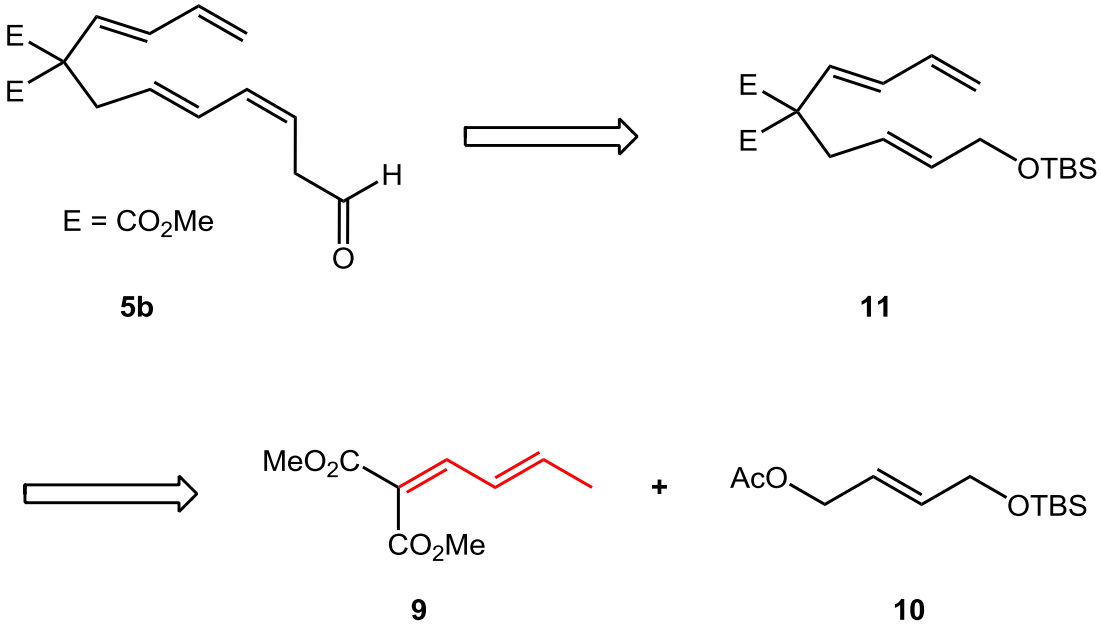


Retrosynthetic Analysis for (±)-Epiglobulol



Sato, Y. *et al. Tetrahedron Lett.* **2006**, *47*, 5617

Retrosynthetic analysis for (±)-Epiglobulol



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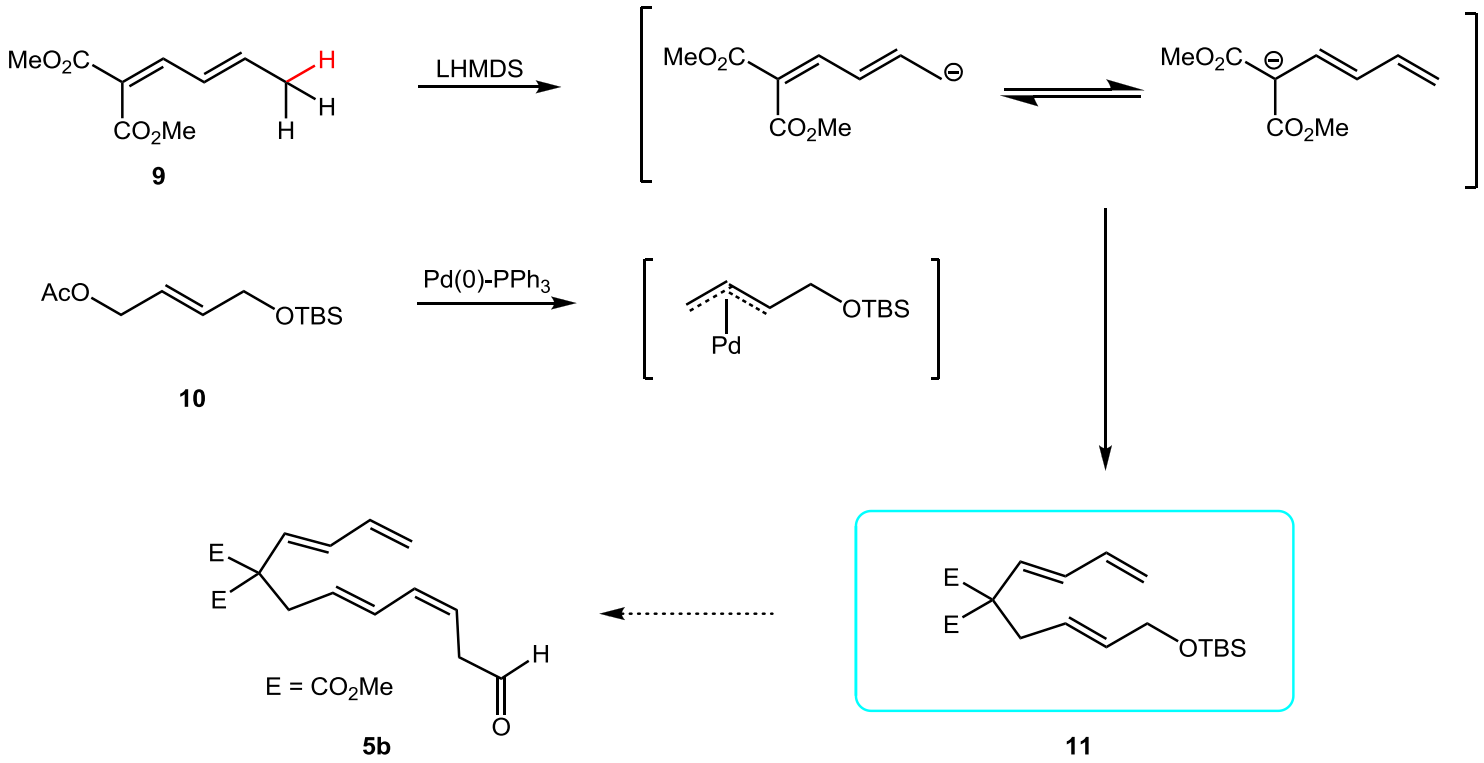

Sato, Y. *et al. Tetrahedron Lett.* **2006**, *47*, 5617

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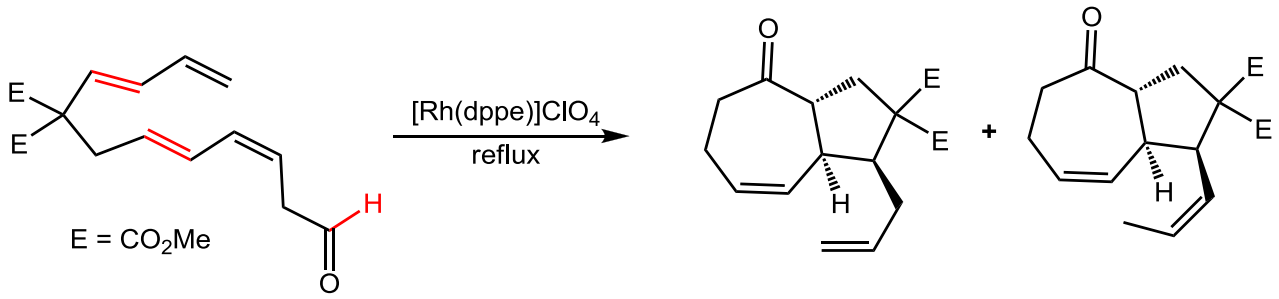
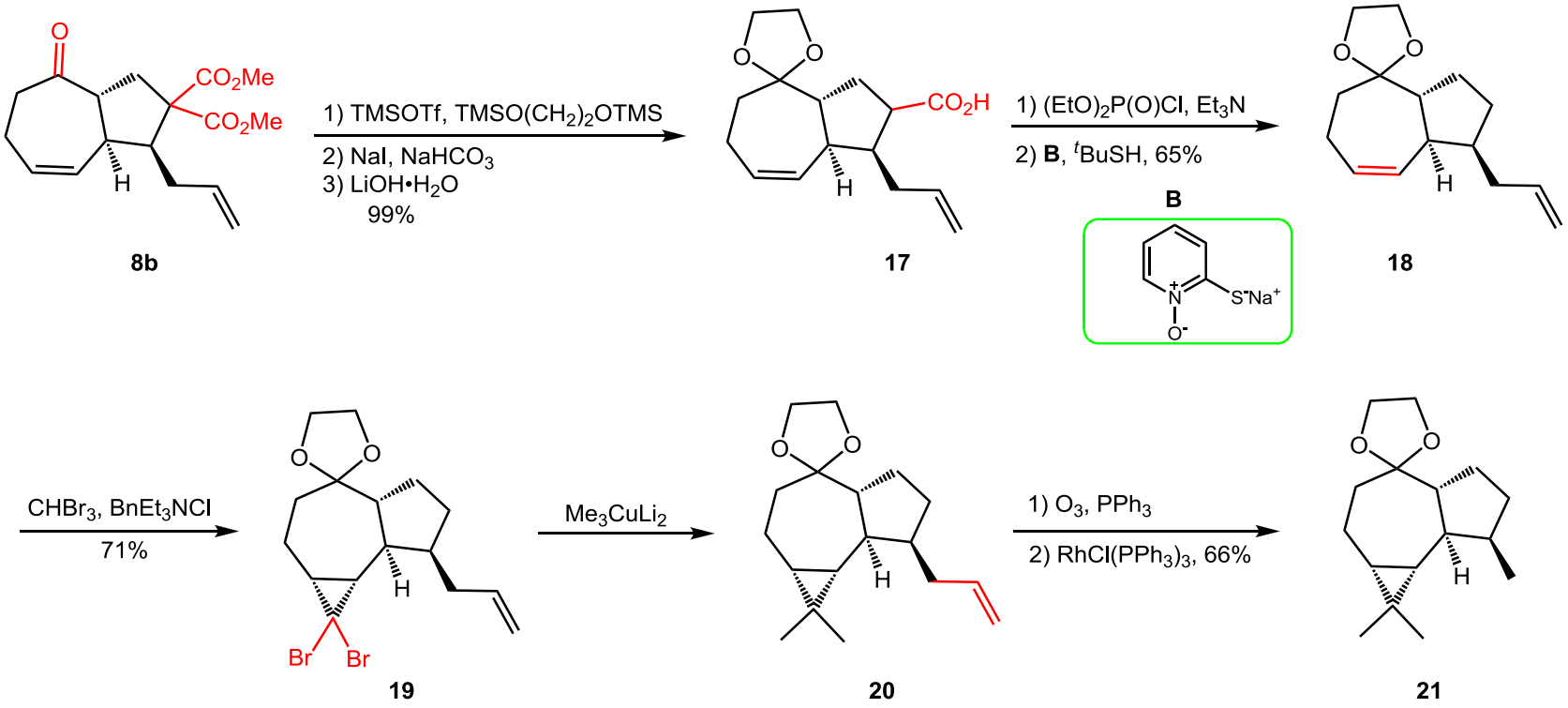


5b **8b** **8b'**

44% 0%

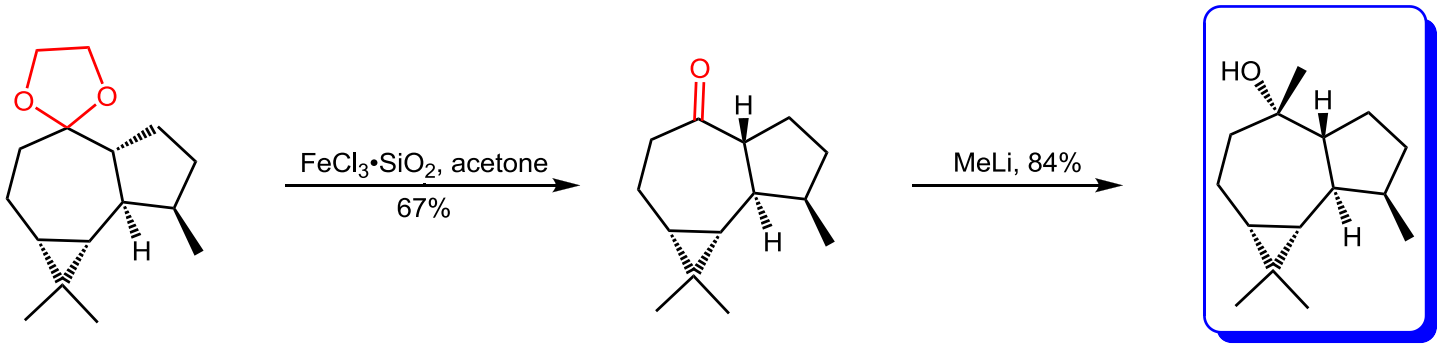
Interesting result

3. Total synthesis by Sato



Sato, Y. *et al. Tetrahedron Lett.* **2006**, *47*, 5617

3. Total synthesis by Sato



Sato, Y. *et al. Tetrahedron Lett.* **2006**, *47*, 5617

小结

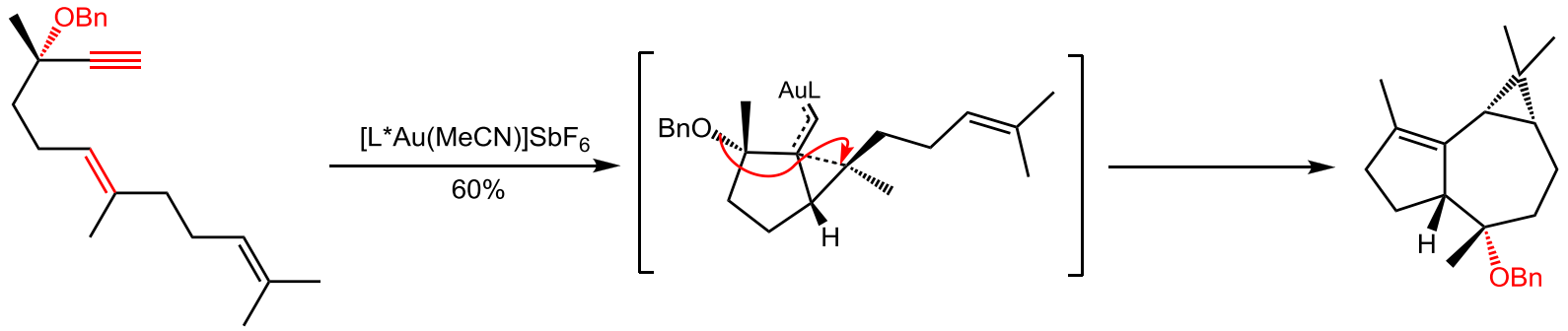
1. **Gupton’s work:**

先构建环丙烷的三元环，再通过光化学重排反应来同时构建一个五元环和一个七元环 。

2. **Sato’s work:**

先通过Rh(I) 催化的氢酰化、环异构化一步构建出一个五元环和一个七元环, 然后再构建环丙烷的三元环。

4. Total synthesis by Echavarren



(*S*,*E*)-**6**

7

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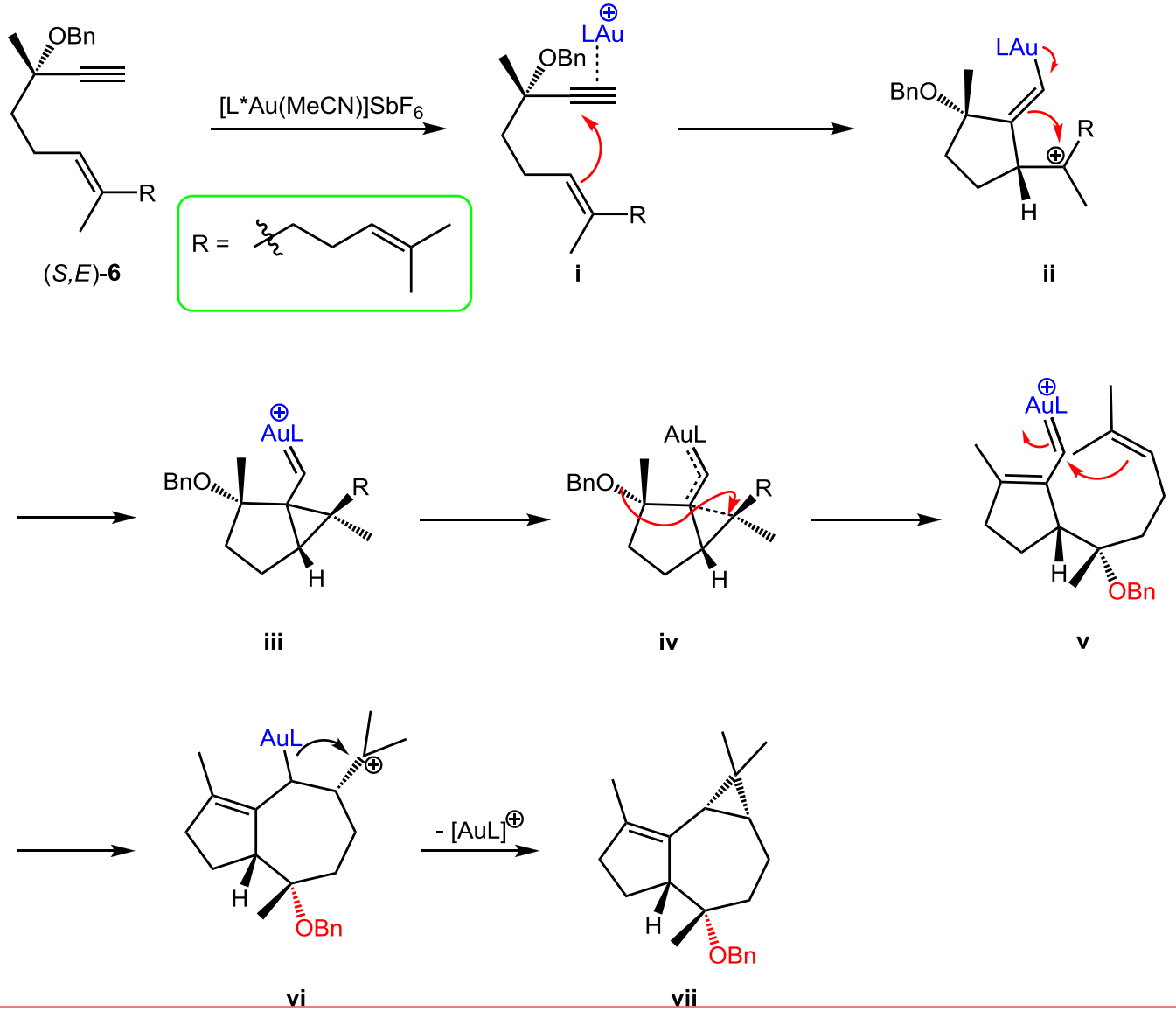
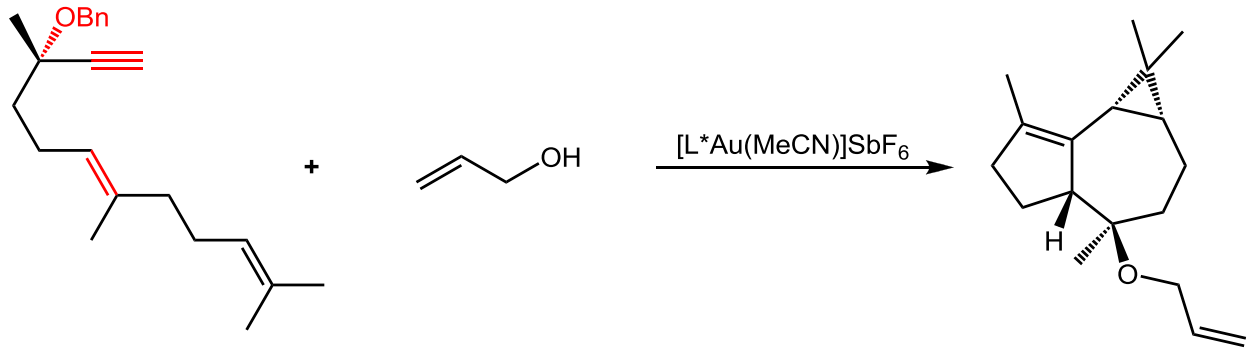
Possible mechanism





(*S,E*)-**6**

8

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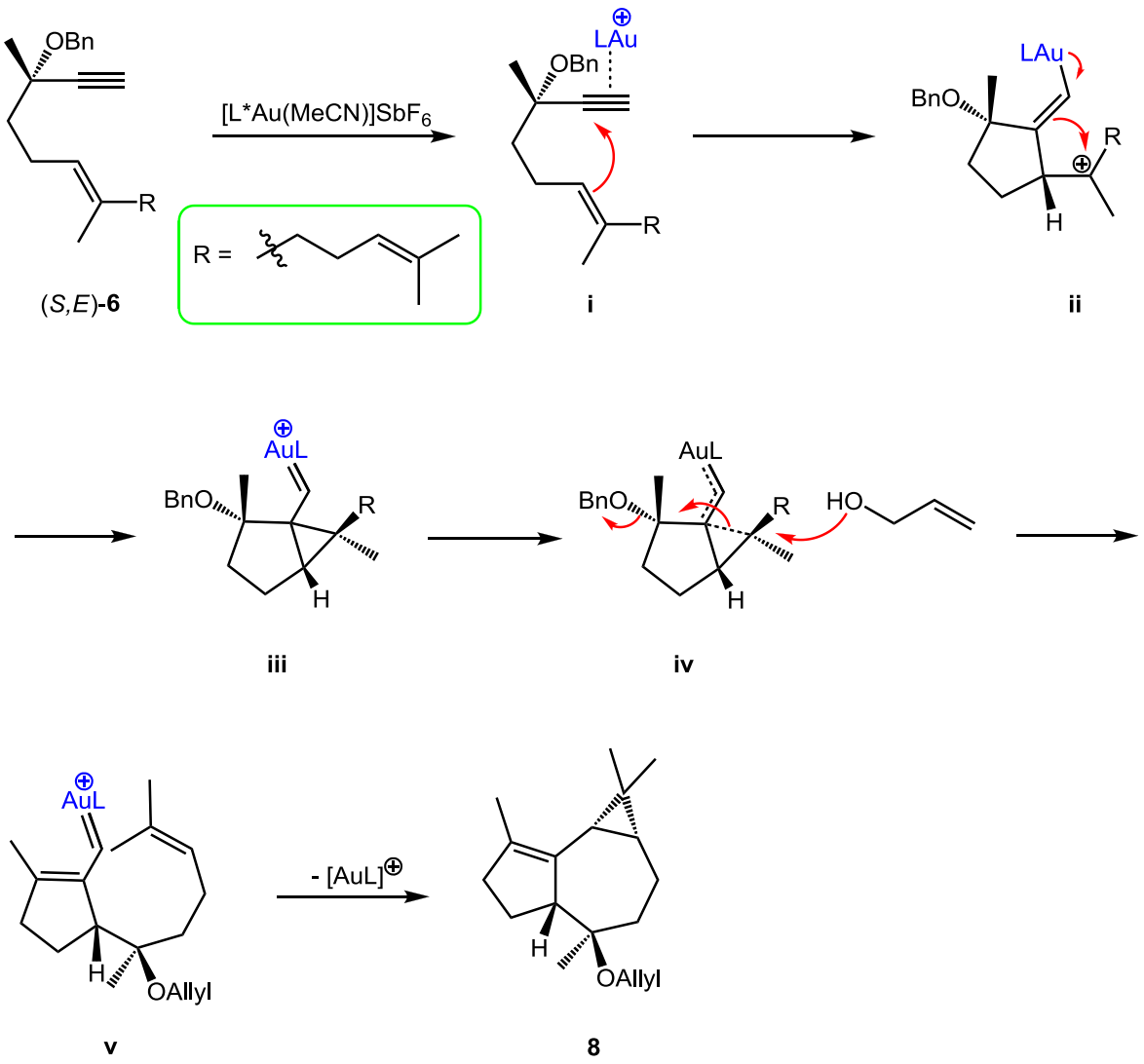
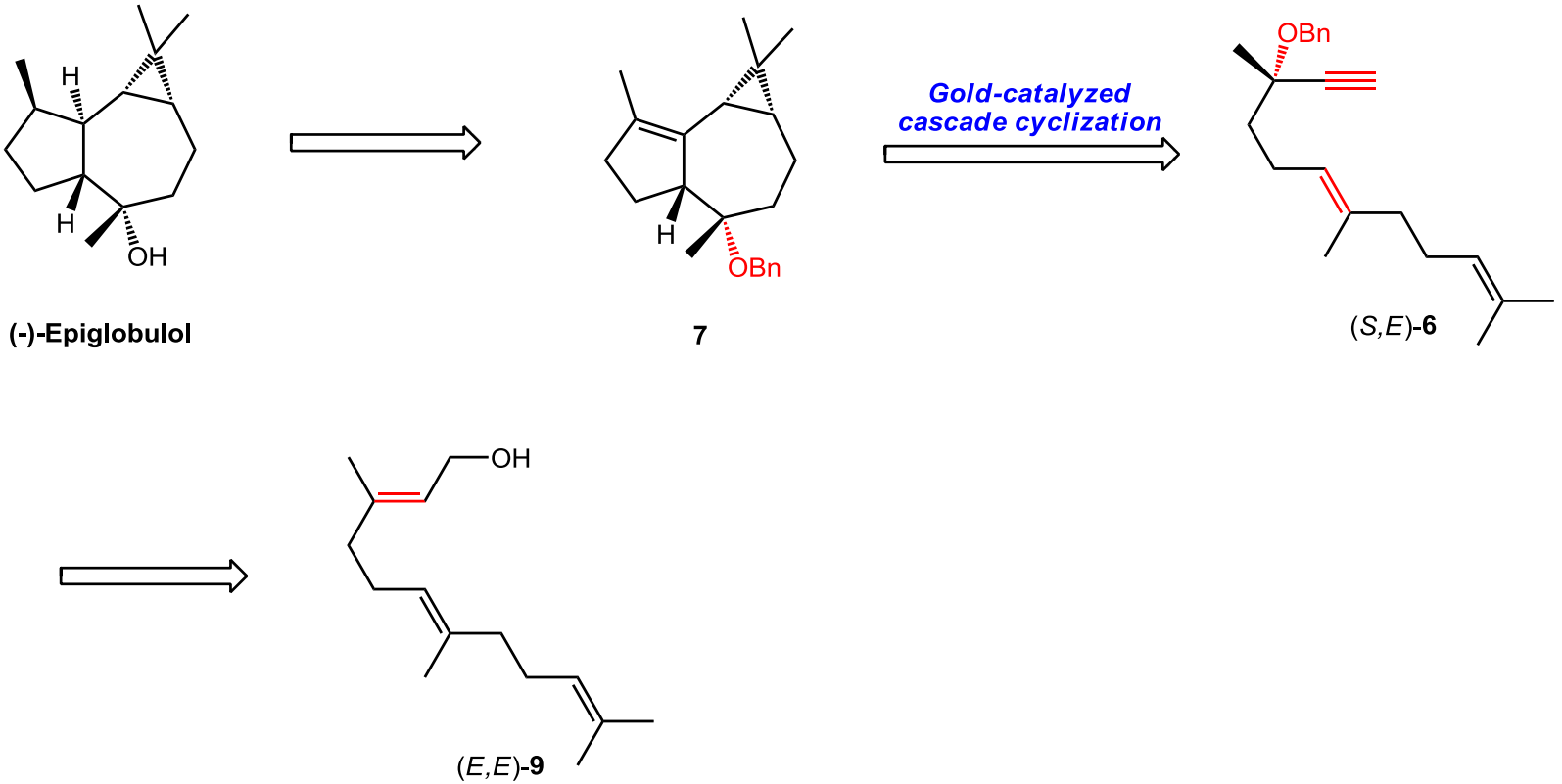
Possible mechanism



Retrosynthetic Analysis



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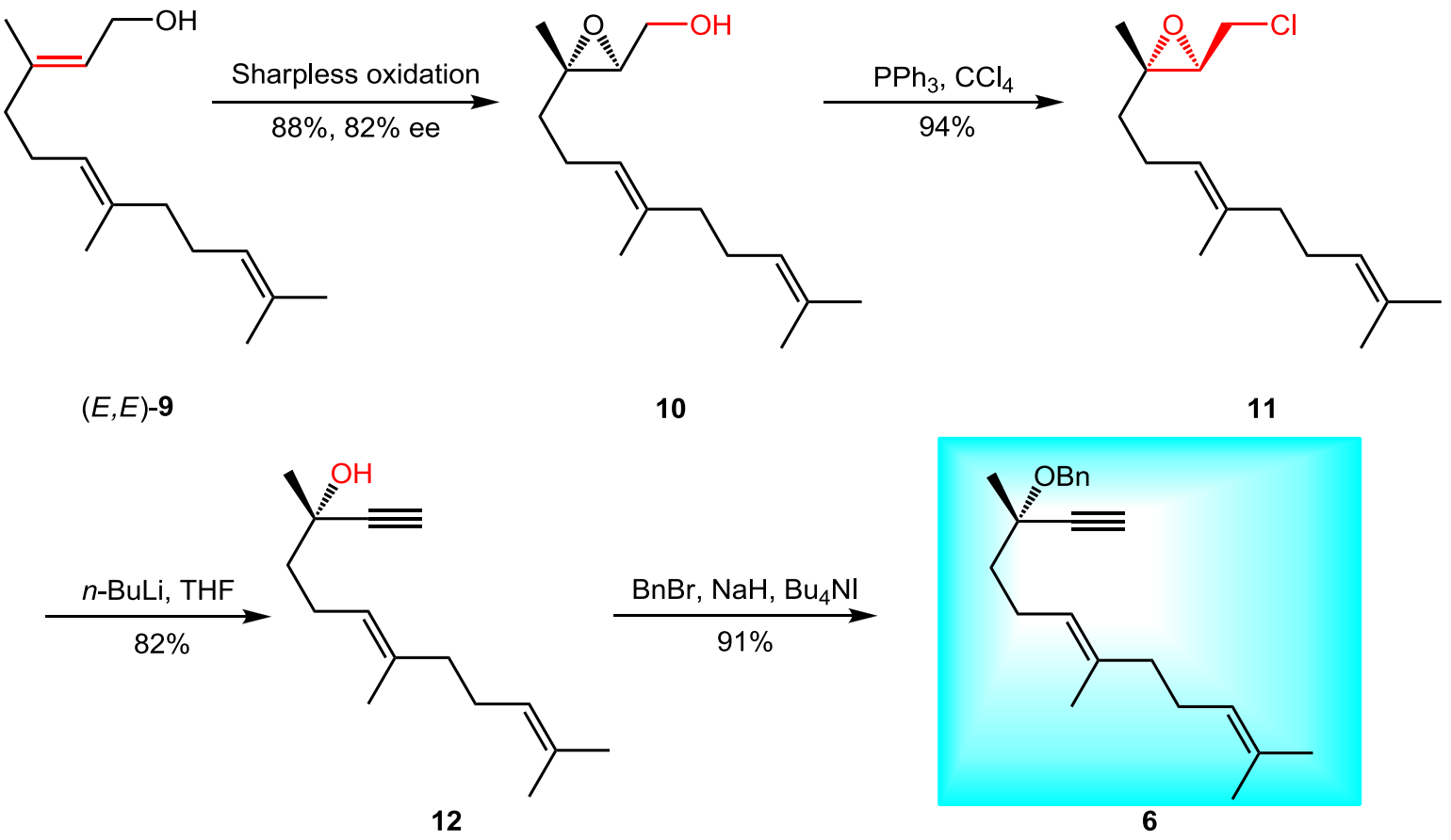
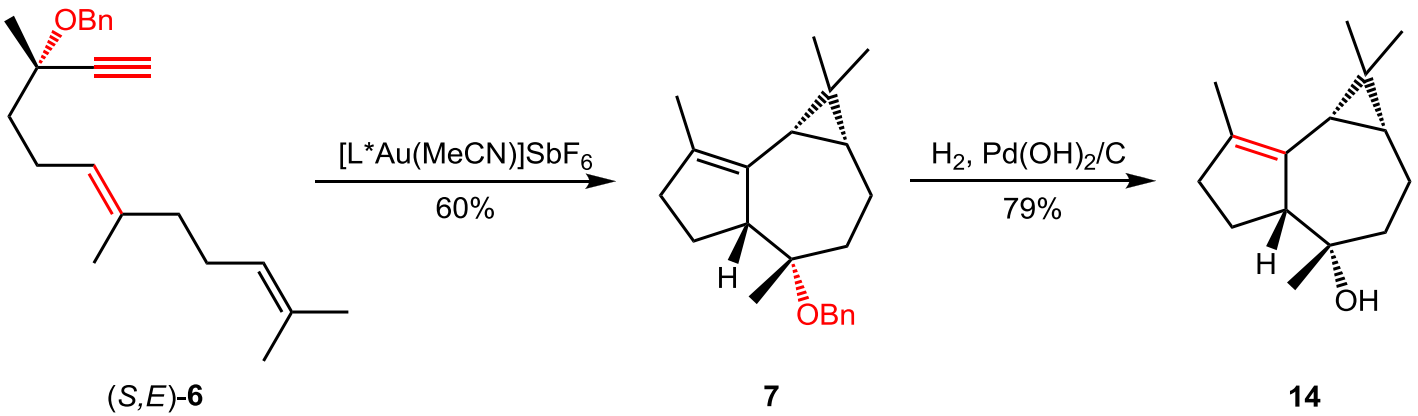
Total synthesis

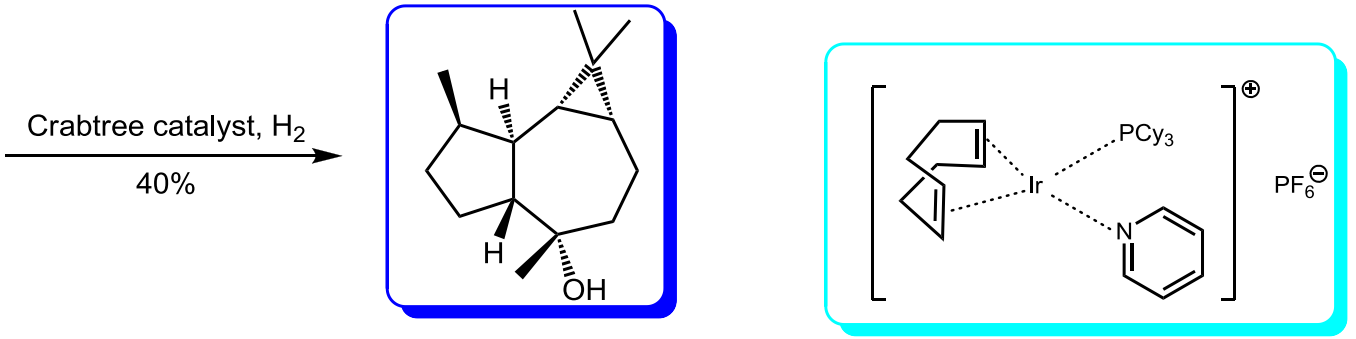


4-step, 62% overall yield

The synthesis of (-)-Epiglobulol

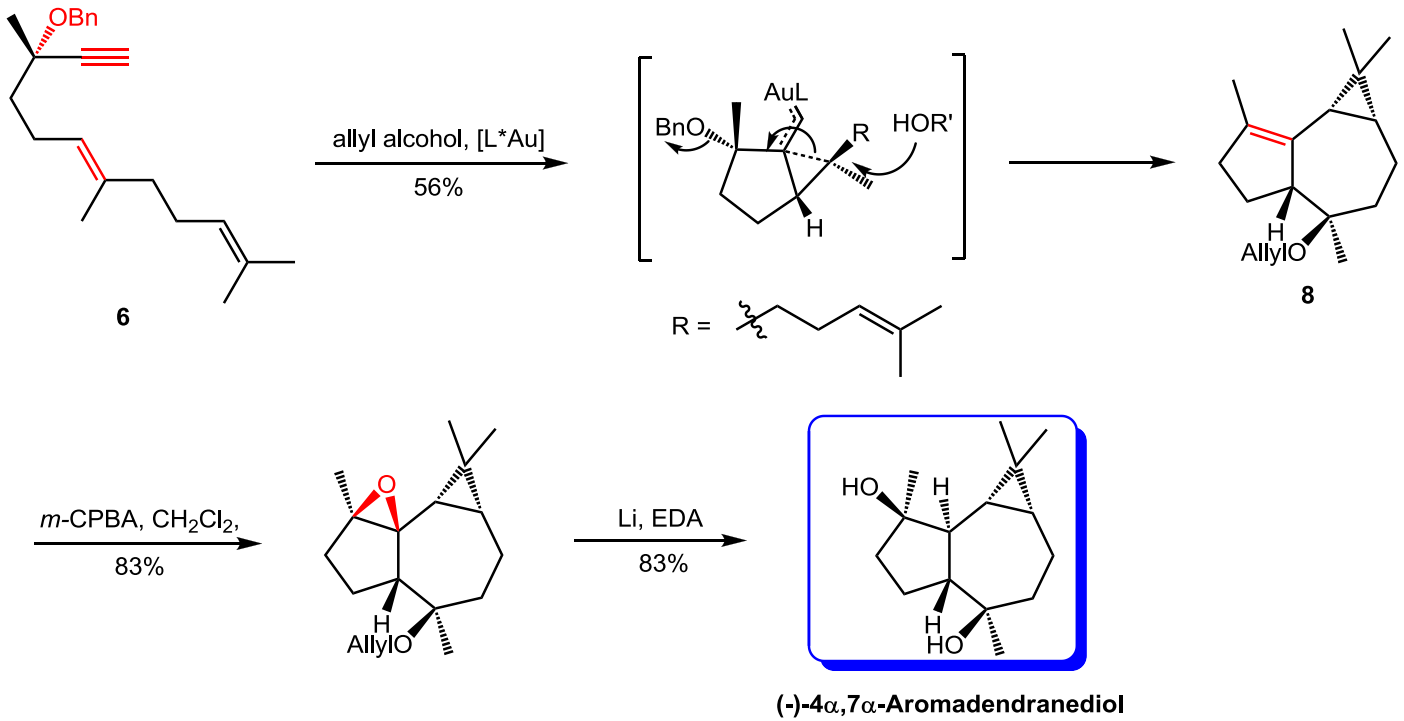


(*S*,*E*)-**6** **7** **14**



(-)-Epiglobulol **Crabtree catalyst**

(-)-4α,7α-Aromadendranediol



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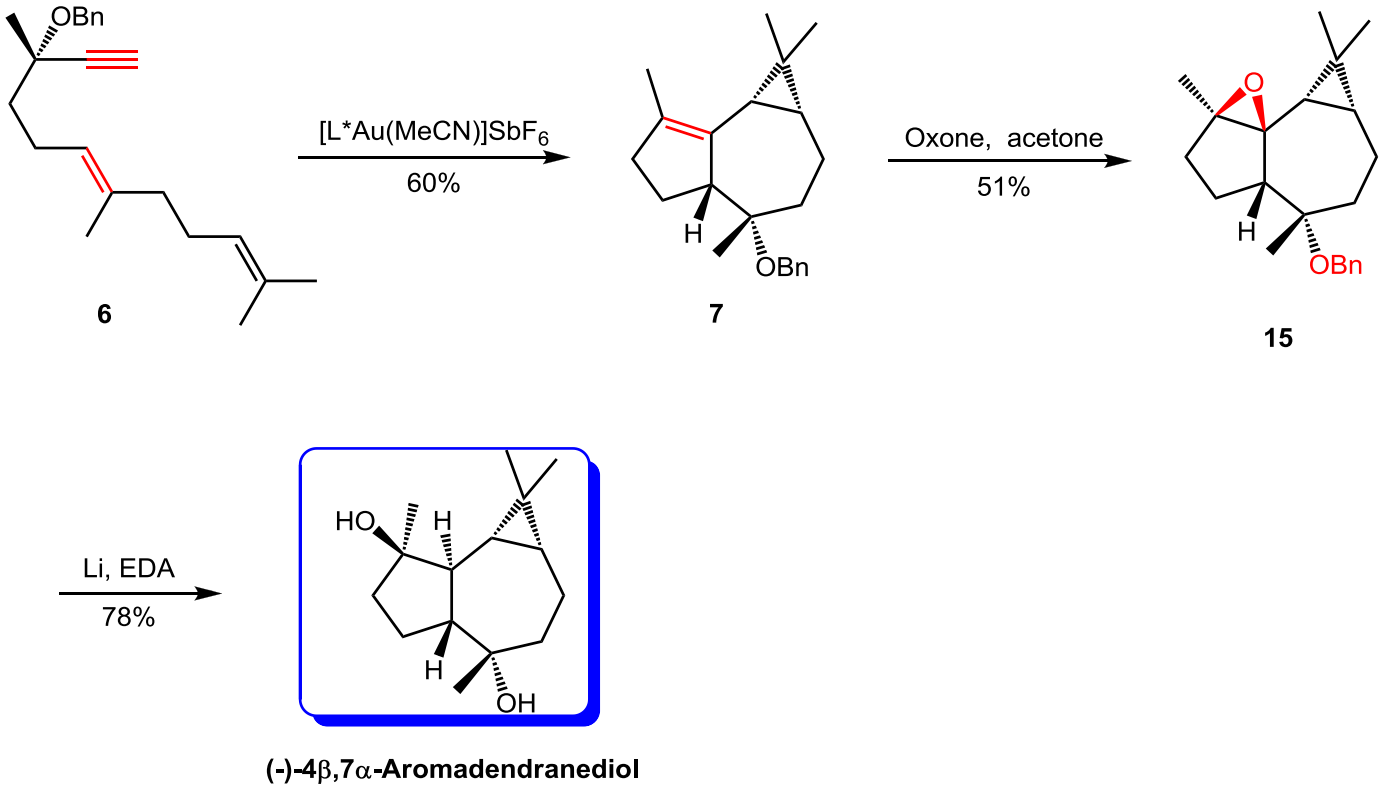
(-)-4β,7α-Aromadendranediol

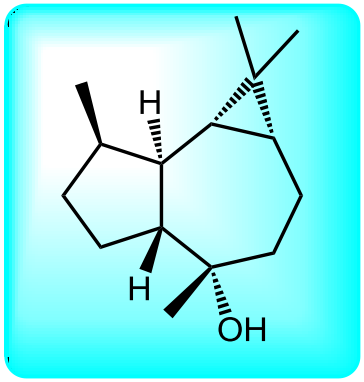


(-)-4β,7α-Aromadendranediol

Oxone ----过硫酸氢钾复合盐，是一种自由流动的白色颗粒状过氧化物，由过硫酸氢钾、硫酸氢钾和硫酸钾组成，是稳定、方便，具有广泛用途的优秀的酸性氧化剂和消毒剂。

5. Summary

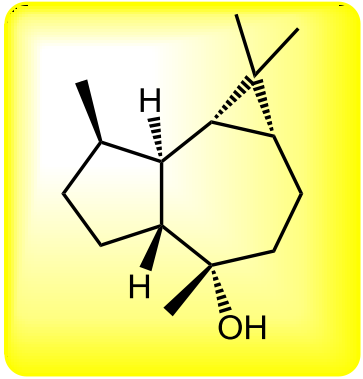
The Gupton's work in 1975



(-)-Epiglobuol

- First total synthesis
- Photochemical rearrangement
- 8 steps, 4% overall yield

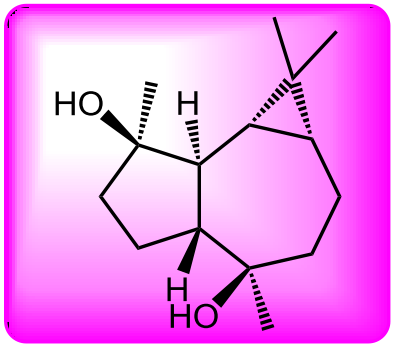
The Sato's work in 2006



(±)-Epiglobuol

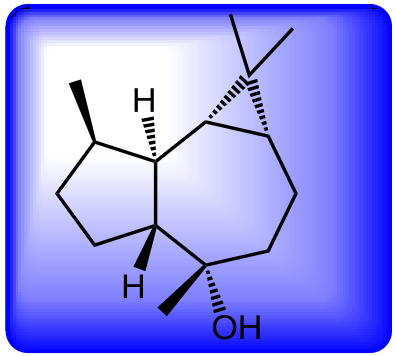
- Racemic version
- Rh(I) catalyzed hydroacylation /Cycloismerization
- 18 steps, 7% overall yield

The Echavarren's work in 2014



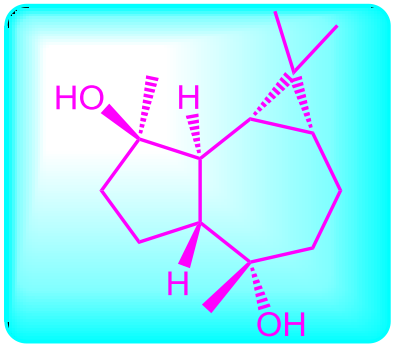
(-)-4α,7α-Aromadendranediol

7 steps
17% overall yield



(-)-Epiglobuol

7 steps
12% overall yield



(-)-4β,7α-Aromadendranediol

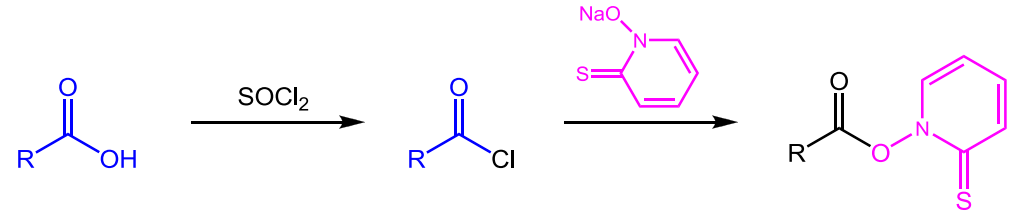
7 steps
15% overall yield

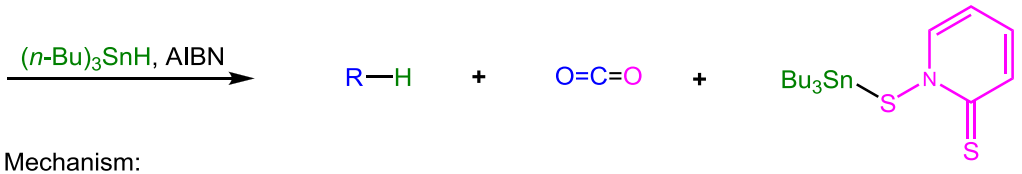
金催化一步构建一个五元环并一个七元环及一个三元环

Aromadendranes are a family of hydroazulenes named after (+)-aromadendrene (**1**), the main component in the essential oil from Eucaliptus trees. The related sesquiterpenoids (-)-globulol (**2**), (-)-epi-globulol (**3**), (-)-4α,7α-aromadendranediol (**4**), and (-)-4β,7α-aromaden-dranediol (**5**) are widespread in plant species and display antifungal, antibacterial，antiviral, cytotoxic, and other activities. Interestingly, the antipodes of **1** and other aromadendrenes have been isolated from corals. Aromadendranes with amino, isonitrile, isothiocyano, and urea functionalities at C4 have been found in sponges. Diterpenoids with an aromadendrane structure are also natural products.

In summary, we have completed highly concise syntheses of three representative aromadendranes from a single precursor by a stereodivergent gold-catalyzed reaction which establishes four new stereogenic centers from a single one. The three natural sesquiterpenes (-)-epiglobulol (**3**), (-)-4α,7α-aromadendranediol (**4**), and (-)-4β,7α-aromadendranediol (**5**) have been synthesized in seven steps in 12, 17, and 15% overall yields, respectively, from commercially available (*E*,*E*)-farnesol (**9**), and constitutes the shortest total syntheses of these natural compounds. This route could be extended for the enantioselective synthesis of any enantiomer of other aromadendranes and non-natural analogues.

Barton 自由基脱羧反应





Mechanism: