

Literature Report II

Asymmetric Total Synthesis of Bufospirostenin A

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Checker: Mu-Wang Chen

Date: 2020-08-24

Li, C.-C. *et al. J. Am. Chem. Soc.* **2020**, 142, 12602.

CV of Professor Li. C.-C



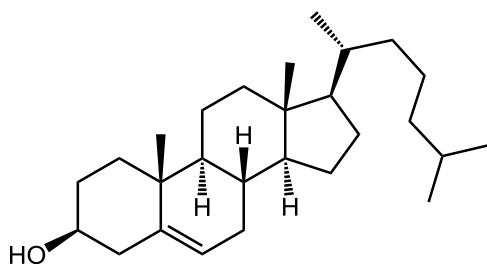
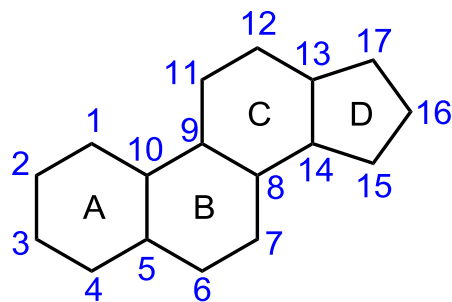
Background:

- ❑ **1997-2001** B.S., China Agricultural University;
- ❑ **2001-2006** Ph.D., Peking University;
- ❑ **2006-2008** Postdoc., The Scripps Research Institute;
- ❑ **2008-2013** Associate Professor, Shenzhen Graduate School, Peking University;
- ❑ **2013-Now** Professor, South University of Science and Technology.

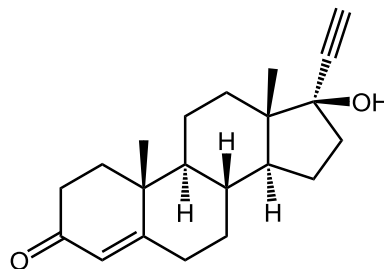
Research:

- Research on total synthesis of complex natural products;
- Research on novel synthetic methodologies for natural products;
- The study of chemical biology and medicinal chemistry of natural products.

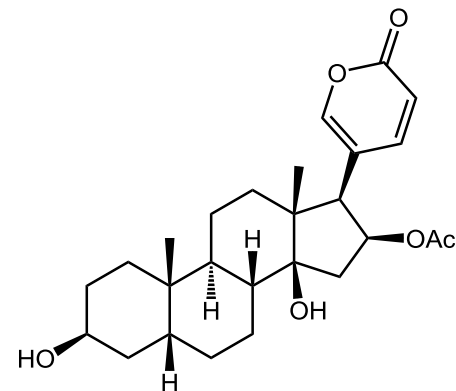
Introduction



Cholesterol

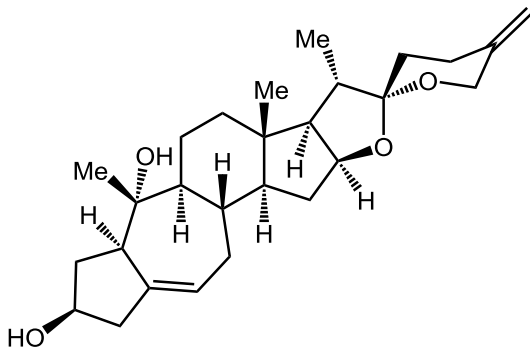


Norethisterone



Bufotaline

Introduction



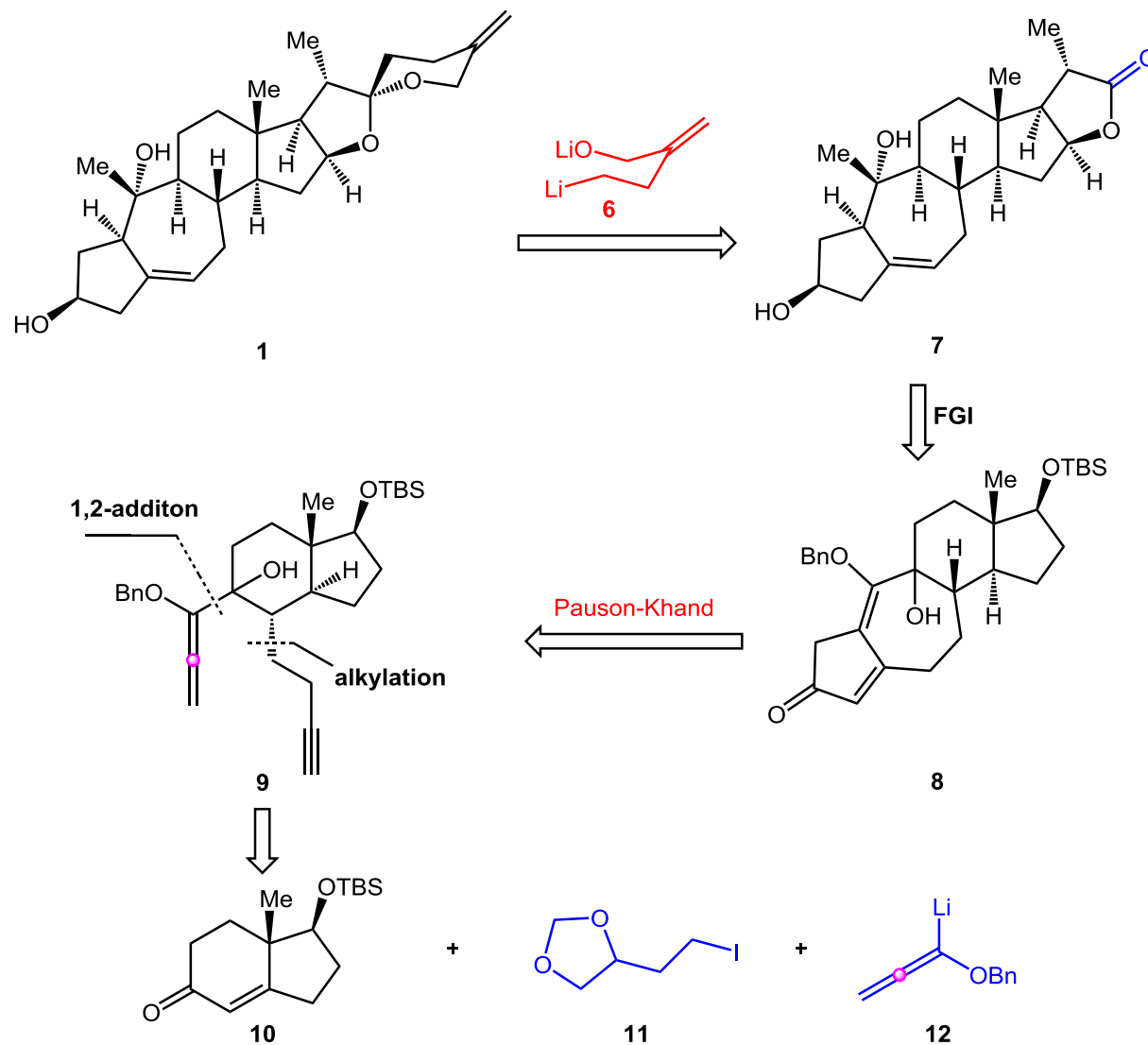
Bufospirostenin A



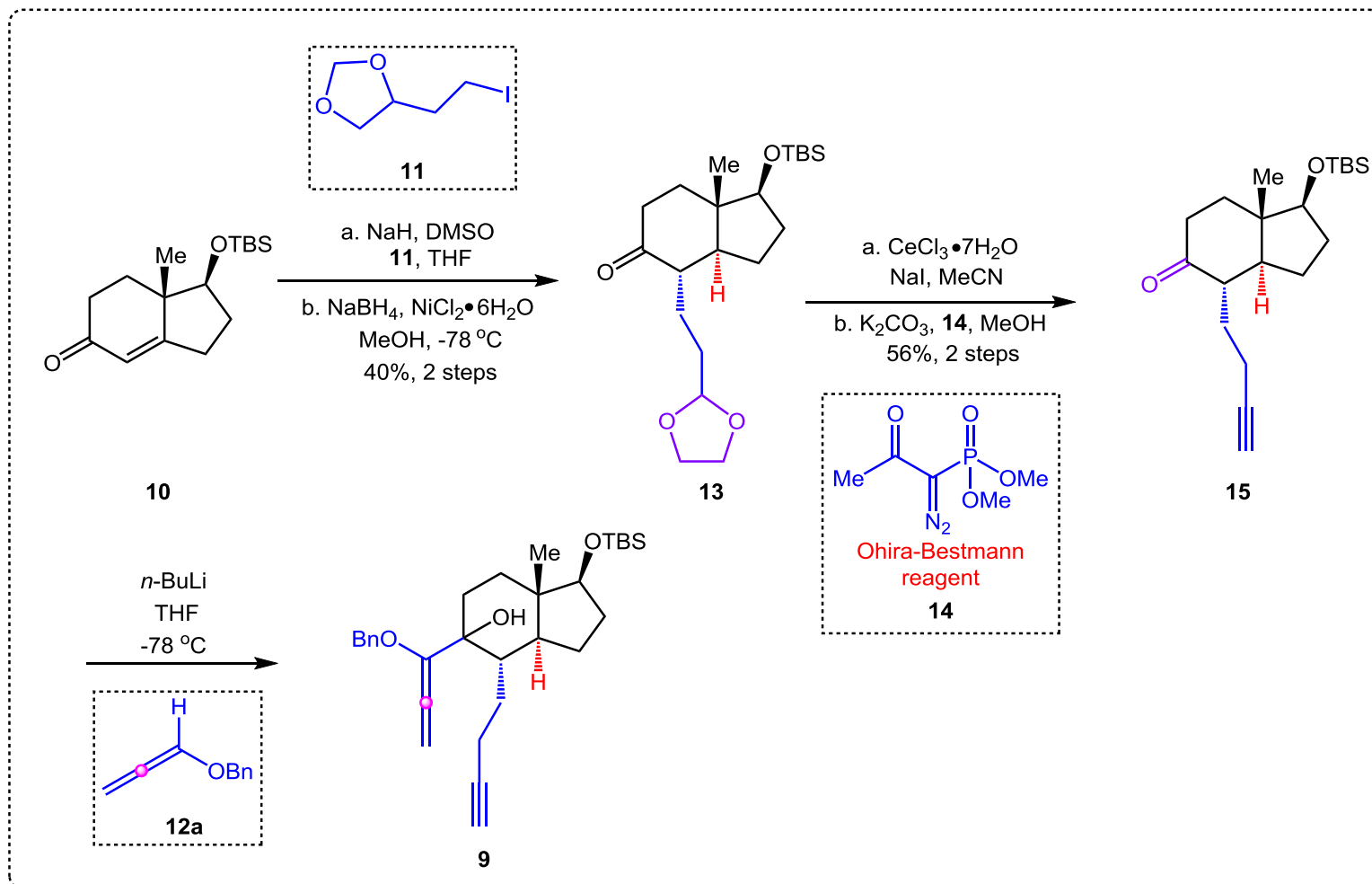
- First spirostanol found in animals;
- Unusual [5-7-6-5-5-6] ring system;
- 11 Stereocenters: 10 contiguous, two quaternary, one spiroketal;
- First total synthesis reported.

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Retrosynthetic Analysis of 1

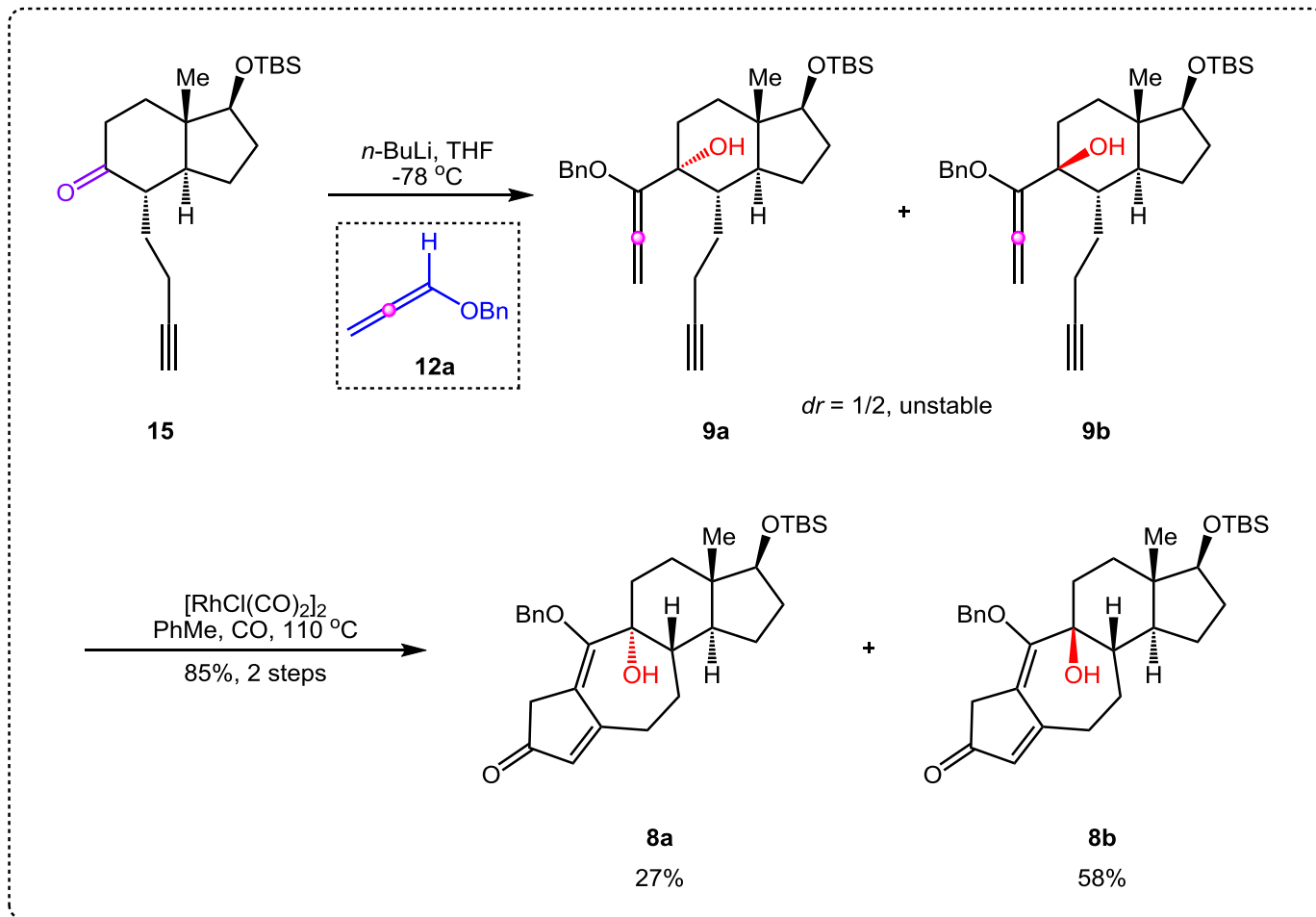


Synthesis of Compound 9

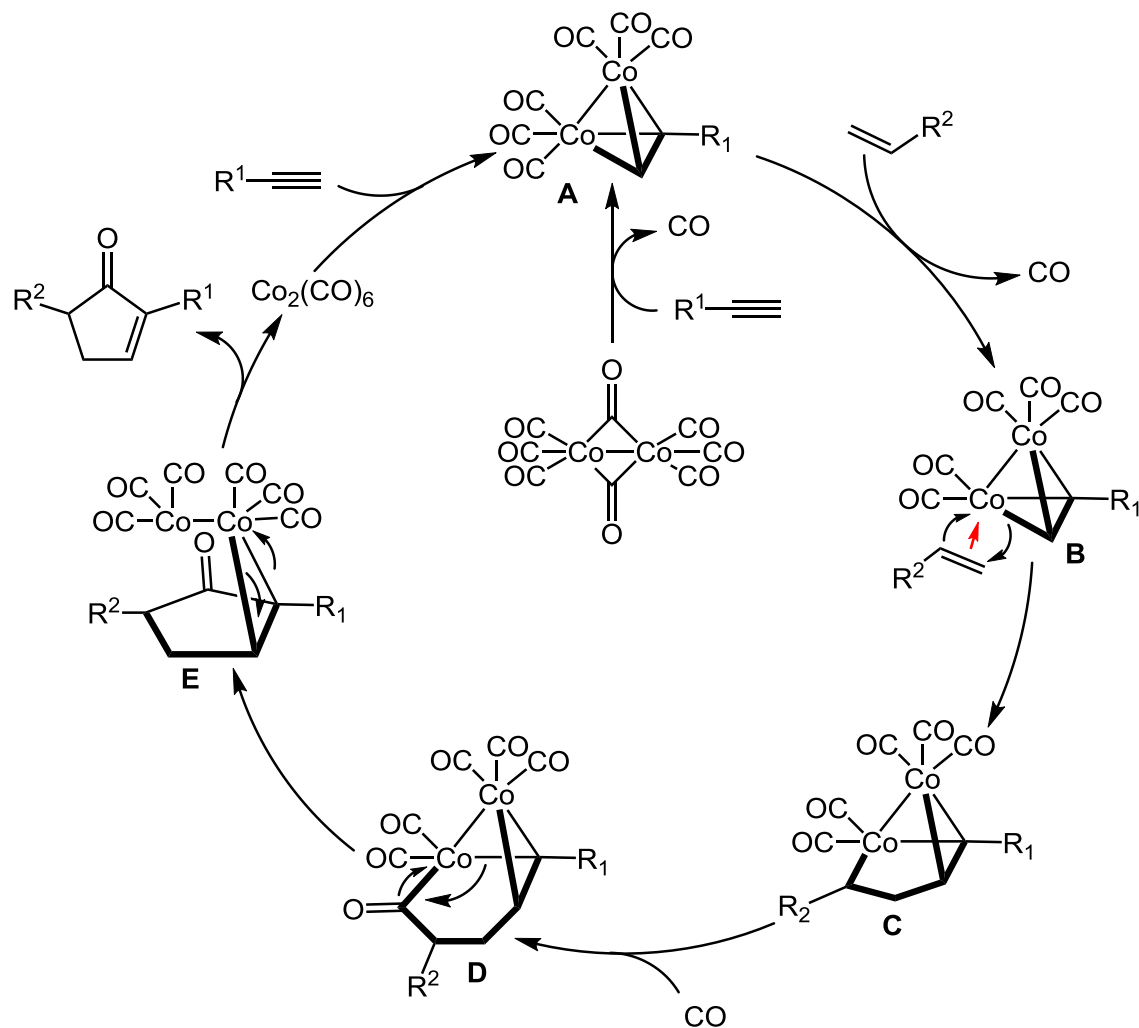
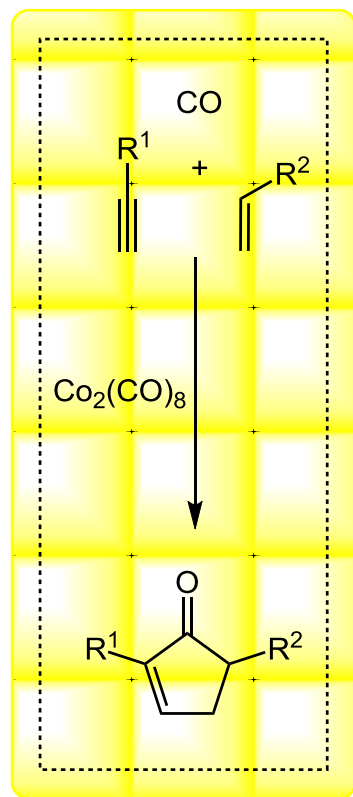


[illegible]

Synthesis of Compound 8

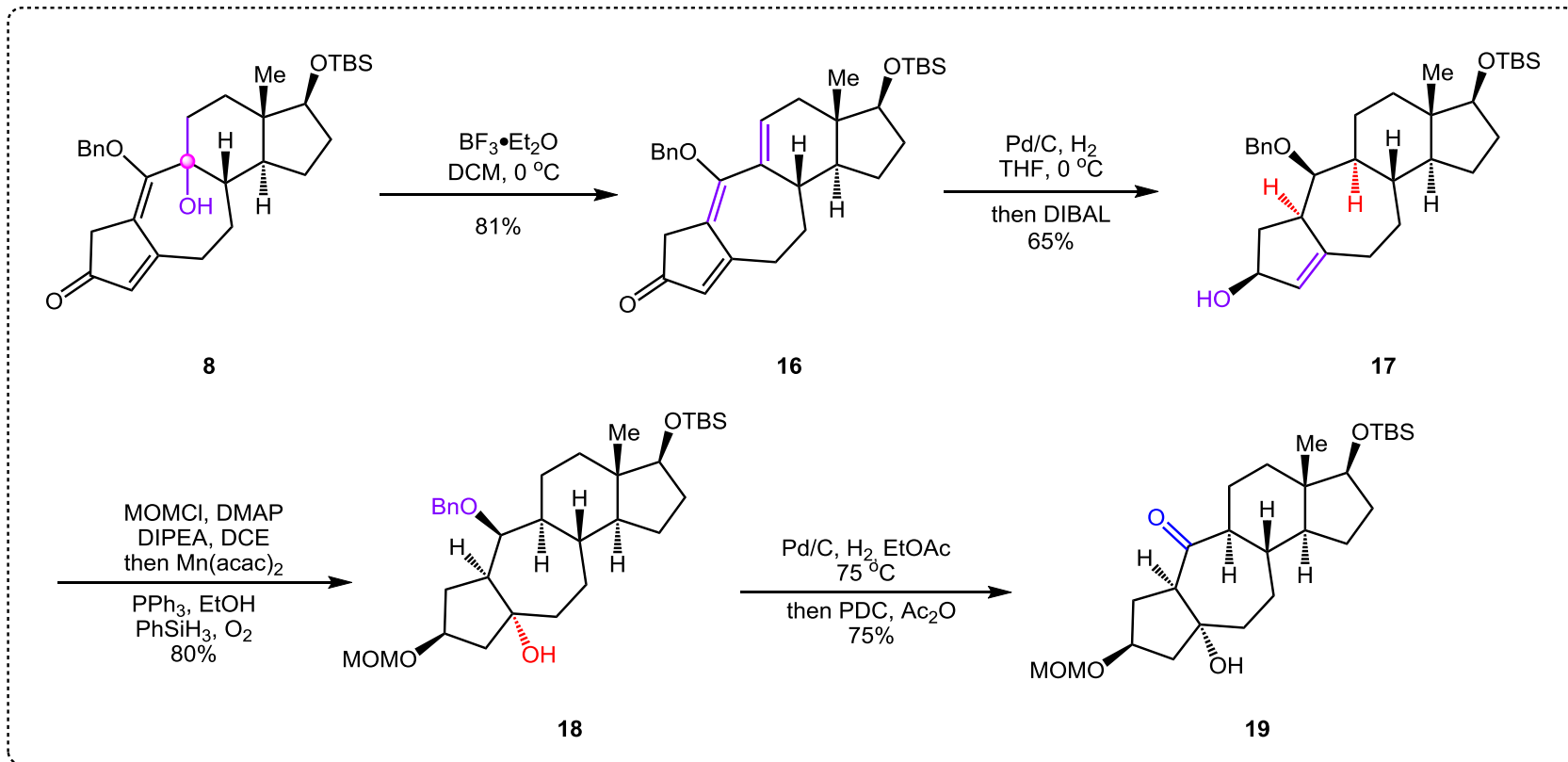


Pauson-Khand Reaction

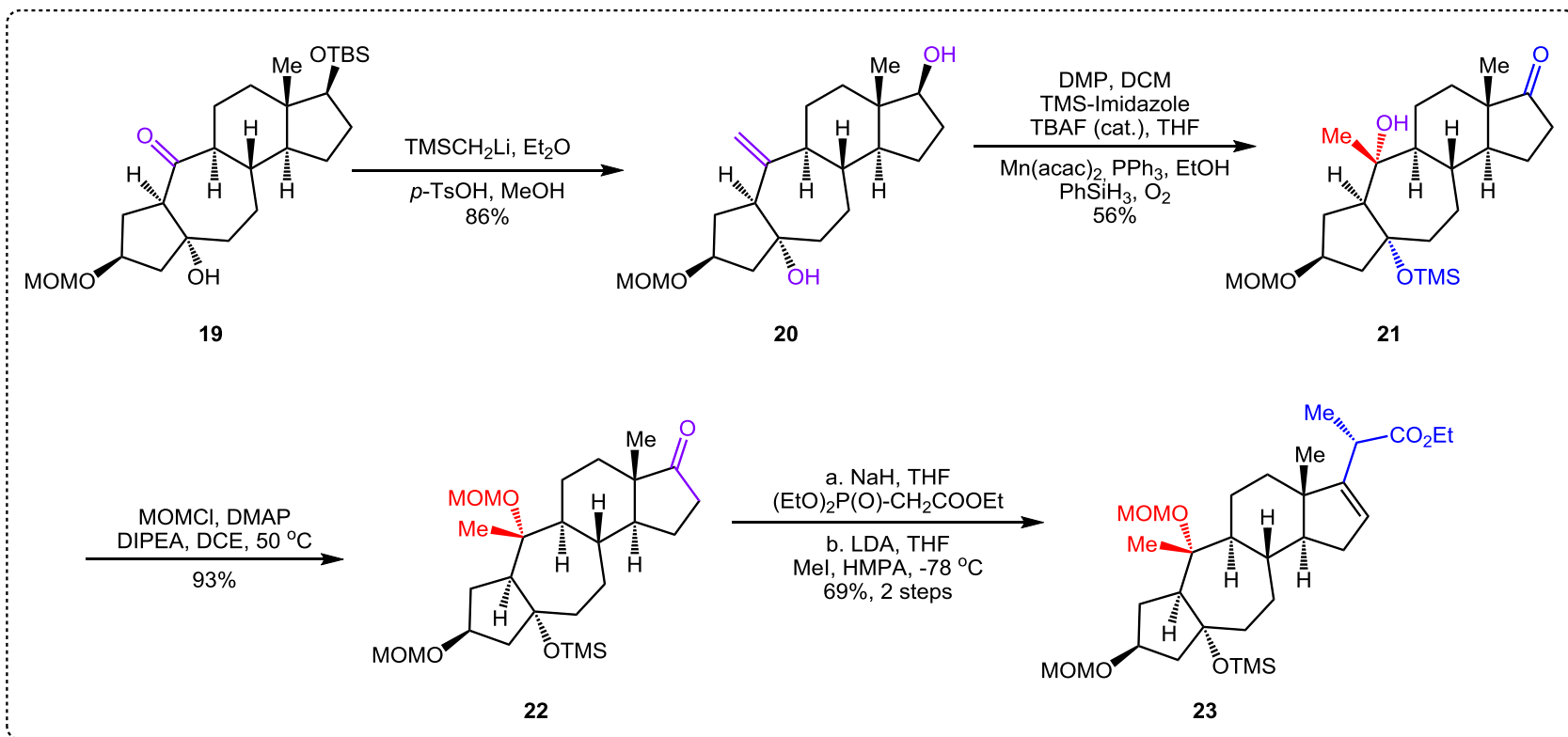


From Name Reaction

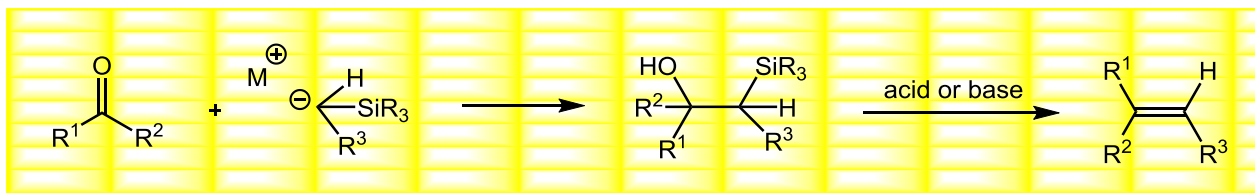
Synthesis of Compound 19



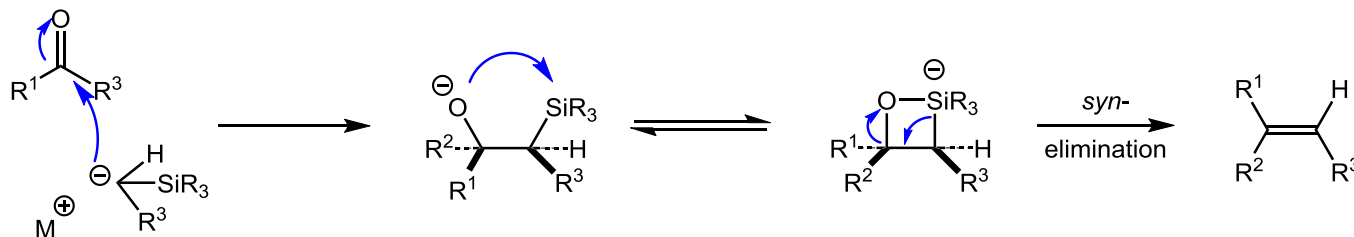
Synthesis of Compound 23



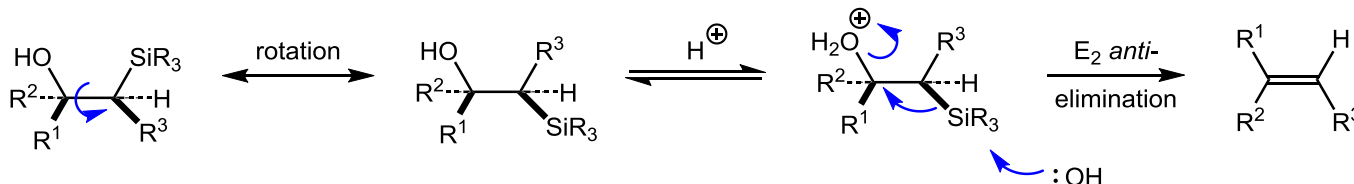
Peterson Olefination



Base conditions :

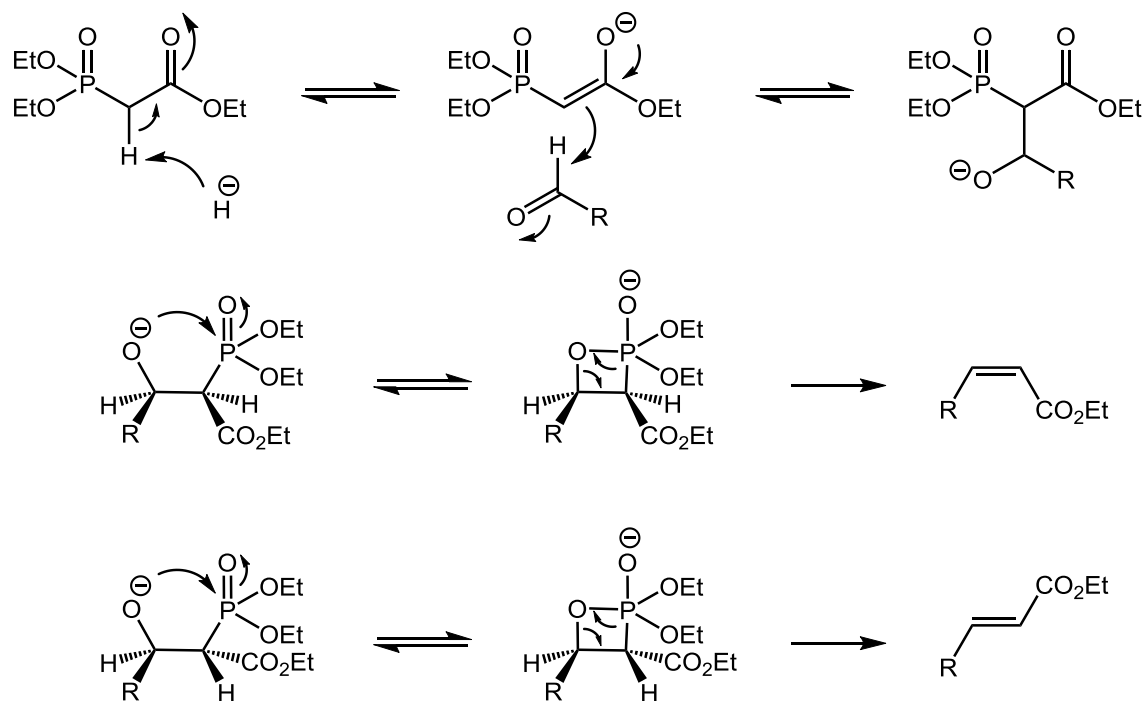
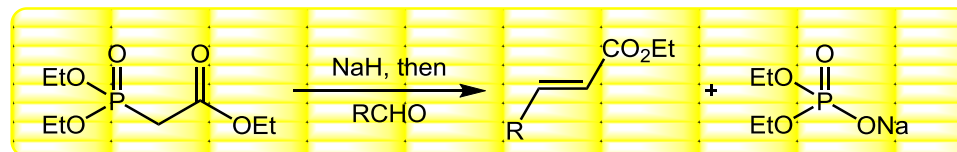


Acidic conditions :



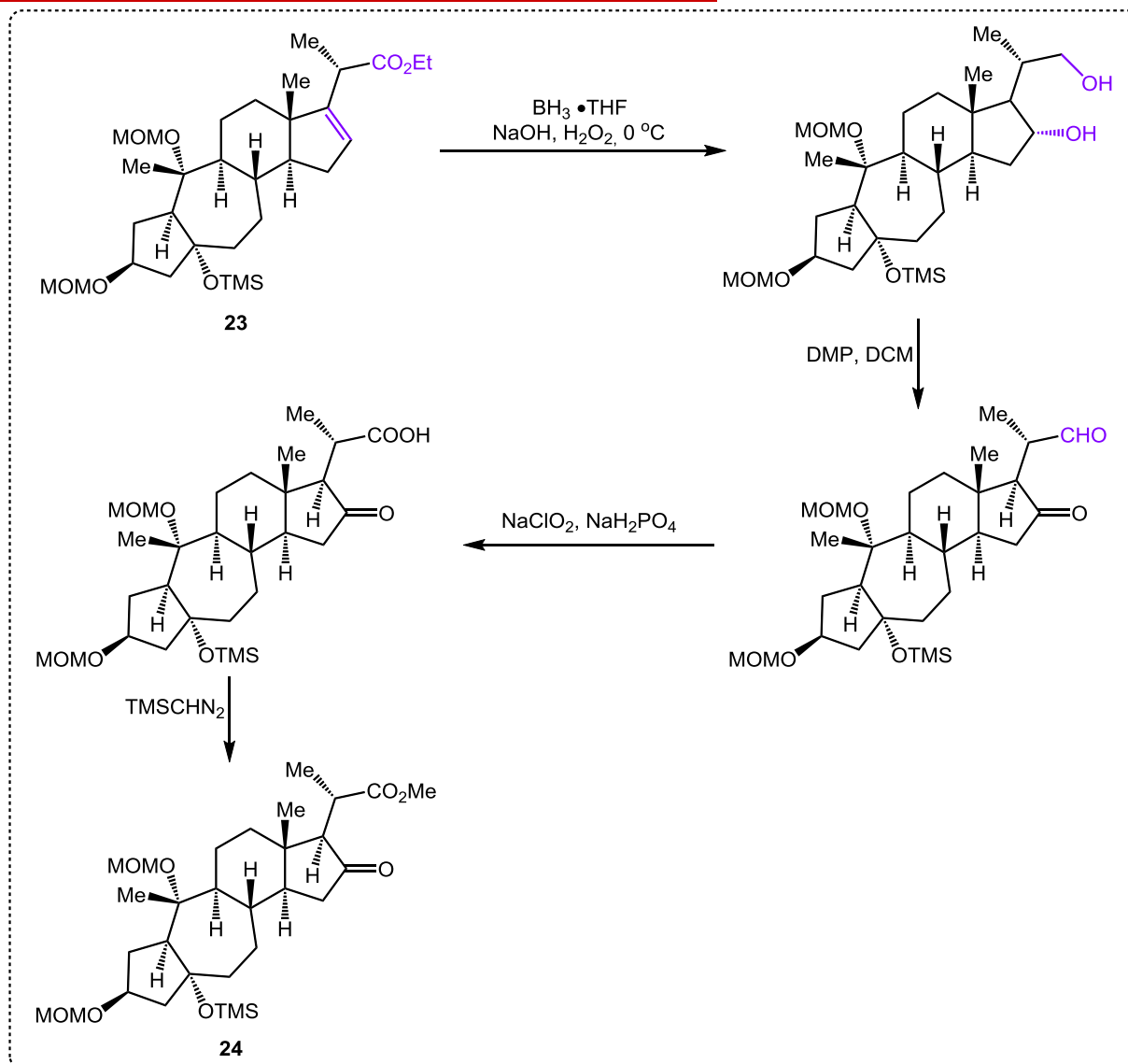
From Name Reaction

Horner-Wadsworth-Emmons Olefination

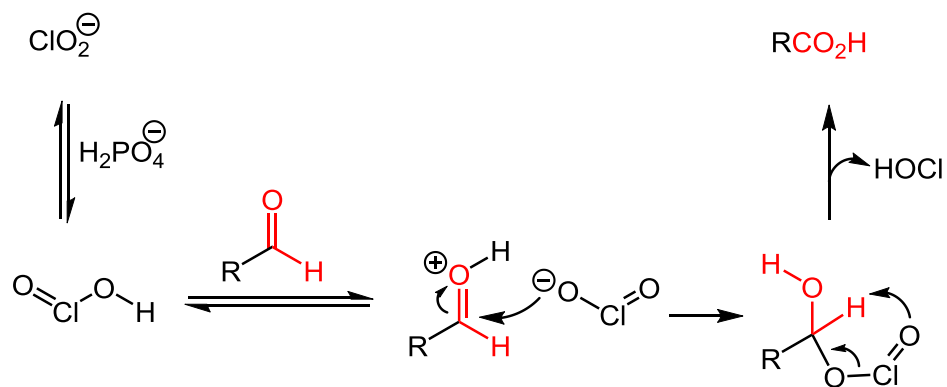
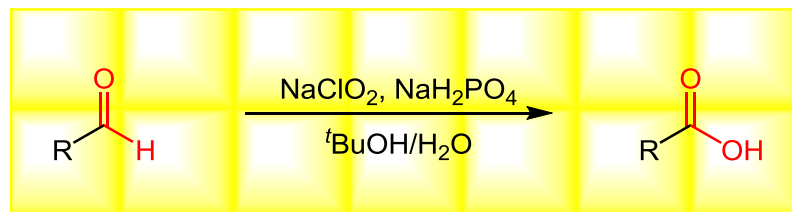


From Name Reaction

Synthesis of Compound 24

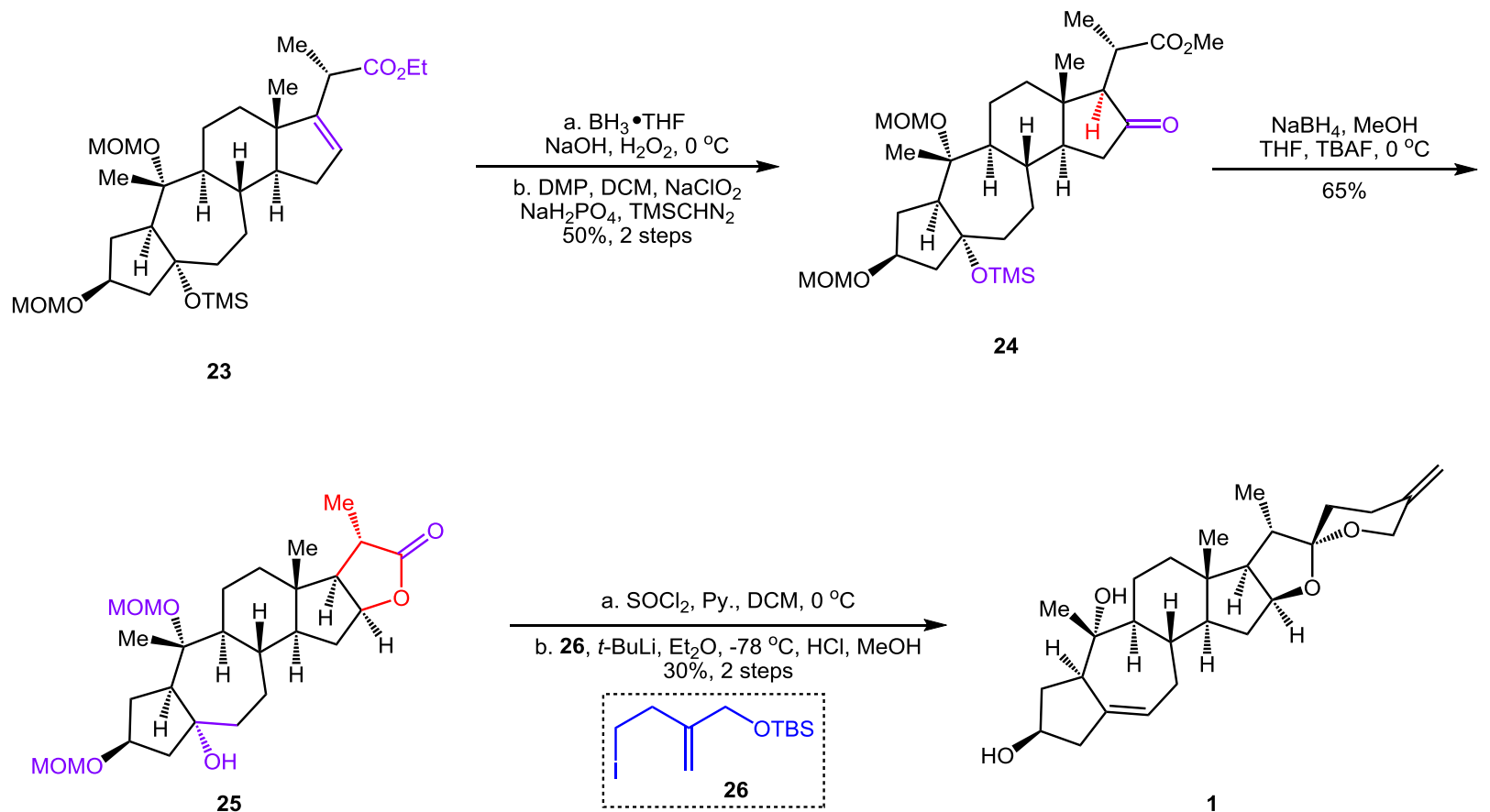


Pinnick Oxidation

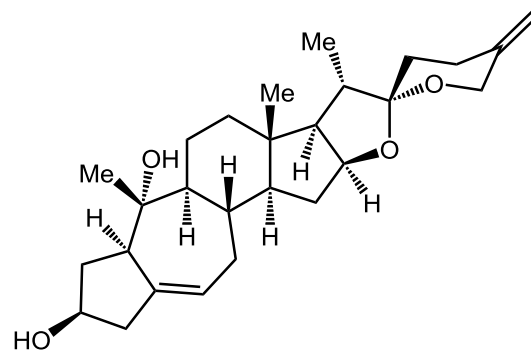


From Name Reaction

Synthesis of Compound 1



Summary



Bufospirostenin A

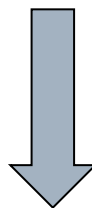
- 20 Total steps, 0.18 % overall yield
- Intramolecular Pauson–Khand reaction
- Mukaiyama hydration

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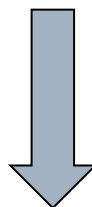
The First Paragraph

Writing Strategy

甾族化合物的重要性



引出作者合成产物具有非常重要的意义



通过分析化合物结构来说明合成任务的艰巨

The First Paragraph

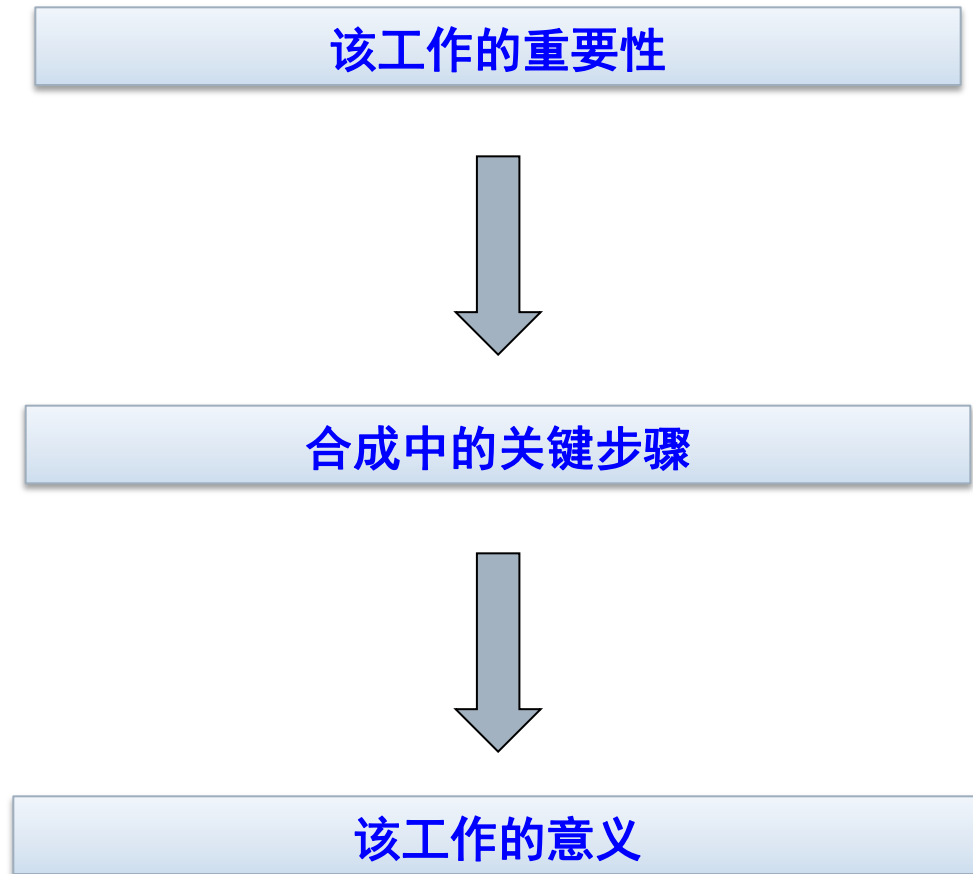
Because of their biological importance and structural diversity, steroid always play an important role in synthetic organic chemistry and drug discovery. Particularly, in recent years, steroids have prompted significant interest from the synthetic community, including the groups of Nagorny, Heretsch, Li, Gui, Kuwahara, Du Bois, Inoue, Baran, and so on. Bufospirostenin A, an unusual steroid with rearranged A/B rings, was isolated by Ye and co-workers in 2017 from the toad *Bufo bufo gargarizans*. The toad *Bufo bufo gargarizans* has long been recognized as an important source in traditional Chinese medicine and is used as valuable anticancer agent in China.

The First Paragraph

With only 1.9 mg (0.004 mol) available, compound **1** has been reported to possess a cardioactive effect and promote blood circulation through causing a 43% inhibition of Na/K ATPase (NKA) at 25 μ m. However, the relative scarcity of bufospirostenin A available from natural sources has impeded a more systematic evaluation of its biological activity. Structurally, bufospirostenin A (**1**) contains an unprecedented and sterically compact [5-7-6-5-5-6] hexacyclic skeleton, and is the first spirostanol known to have a rearranged A/B ring system rather than the usual decalin system. In particular, bufospirostenin A possesses one spiroketal center in the E/F ring system. Therefore, bufospirostenin A presents a formidable synthetic challenge.

The Last Paragraph

Writing Strategy



The Last Paragraph

In summary, we have achieved the first and asymmetric total synthesis of bufospirostenin A via a linear sequence of 20 steps from readily available compound 10. Notably, the synthetically challenging [5-7-6-5] tetracyclic ring system, found in 1 and other natural products, was efficiently synthesized via a unique intramolecular Pauson-Khand reaction. To be the best of our knowledge, this work represents the first example of an intramolecular Pauson-Khand reaction of an alkoxyallene-yne in natural product synthesis. Furthermore, the 11 stereocenters in 1, including the contiguous 10 stereocenters, were constructed diastereoselectively. If *ent*-bufospirostenin A is required, *ent*-10 would be needed.

The Last Paragraph

This strategy will enable the diverse synthesis of bufospirostenin A analogs from various analogs of 10, 11, and 12 to facilitate further biological research, this work is currently underway in our laboratory and will be reported in due course.

Representative Examples

In our continuing efforts toward the synthesis of biologically active abeo-steroid or polycyclic natural products with a 7-membered ring, we herein describe the first and asymmetric total synthesis of bufospirostenin, based on the intramolecular rhodium-catalyzed Pauson-Khand reaction of an alkoxyallene-yne. (在我们对于...的不懈努力下，我们成功报道了...，并基于...的反应)

With compound 19 in hand, we proceeded to next stage of our proposed synthesis of bufospirostenin. (在得到...以后，我们进行下一阶段的合成)

Moving forward, we continued toward the last stage of the synthesis via the diastereoselective installation of the spiroketalization of the spiroketal moiety. (可以应用于最后阶段的工作)

Acknowledgement

***Thanks
for your attention***