

# Literature Report 2

## Total Synthesis of Maoecrystal P: Application of a Strained Bicyclic Synthon

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**Checker: Ji Zhou**

**Date: 2018-4-9**

Su, F.; Lu, Y.; Kong, L.; Liu, J.; Luo, T.\*  
*Angew. Chem. Int. Ed.* **2018**, *57*, 760-764.

# CV of Prof. Tuoping Luo

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## ***Background:***

- **2001-2005** B.S., Peking University
- **2005-2011** Ph.D., Harvard University
- **2011-2013** Postdoctoral Fellow, H3 Biomedicine Company
- **2013-Now** Professor, Peking University

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## ***Research:***

- Efficient synthesis, structural modification and property optimization about highly biologically active natural products and small molecules.
- New research tools about drug target proteins.

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## 2 Total Synthesis of (-)-Hibiscone C

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## 3 Total Synthesis of Lysergine

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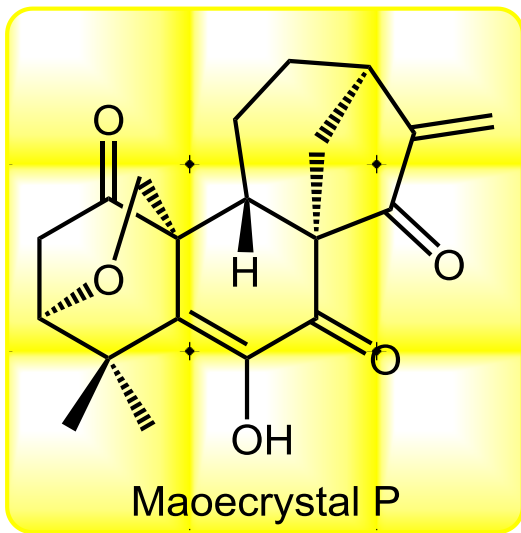
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## 5 Summary

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# Introduction

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**Isodon eriocalyx (毛萼香茶菜)**

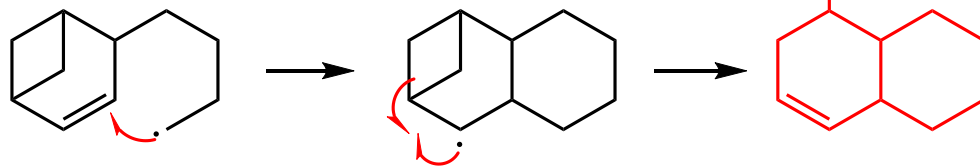
- It belongs to a family of *ent*-kaurene diterpenoids;
- It was first isolated from the the dried leaves of *Isodon eriocalyx*;
- It has shown promising cytotoxicity against human tumor cells.

Wang, J.; Lin, Z.-W.; Zhao, Q.-S.; Sun, H.-D. *Phytochemistry* **1998**, *47*, 307.

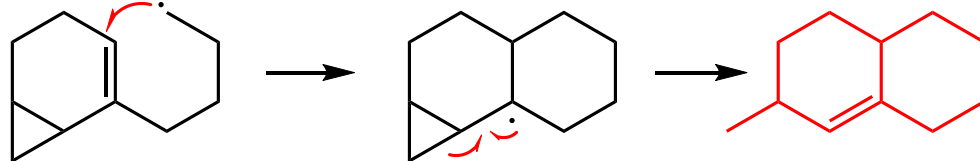
# Two Models of Cyclization

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Type I:  
6-*exo*-trig



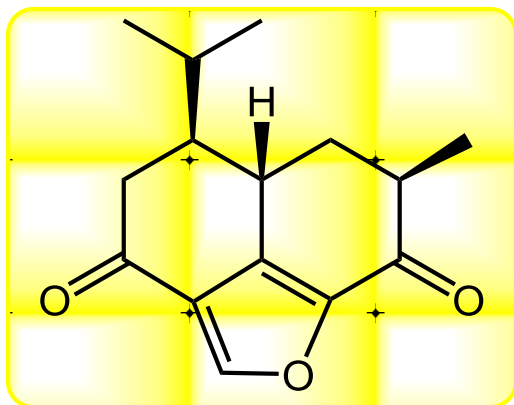
Type II:  
6-*endo*-trig



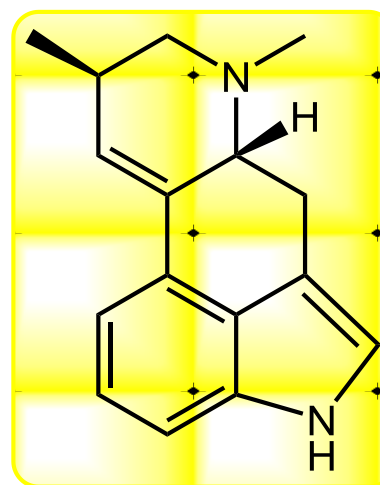
Lu, Y.; Yuan, H.; Zhou, S.; Luo, T. *Org. Lett.* **2017**, *19*, 620.

# Total Syntheses of (-)-Hibiscone C and (±)-Lysergine

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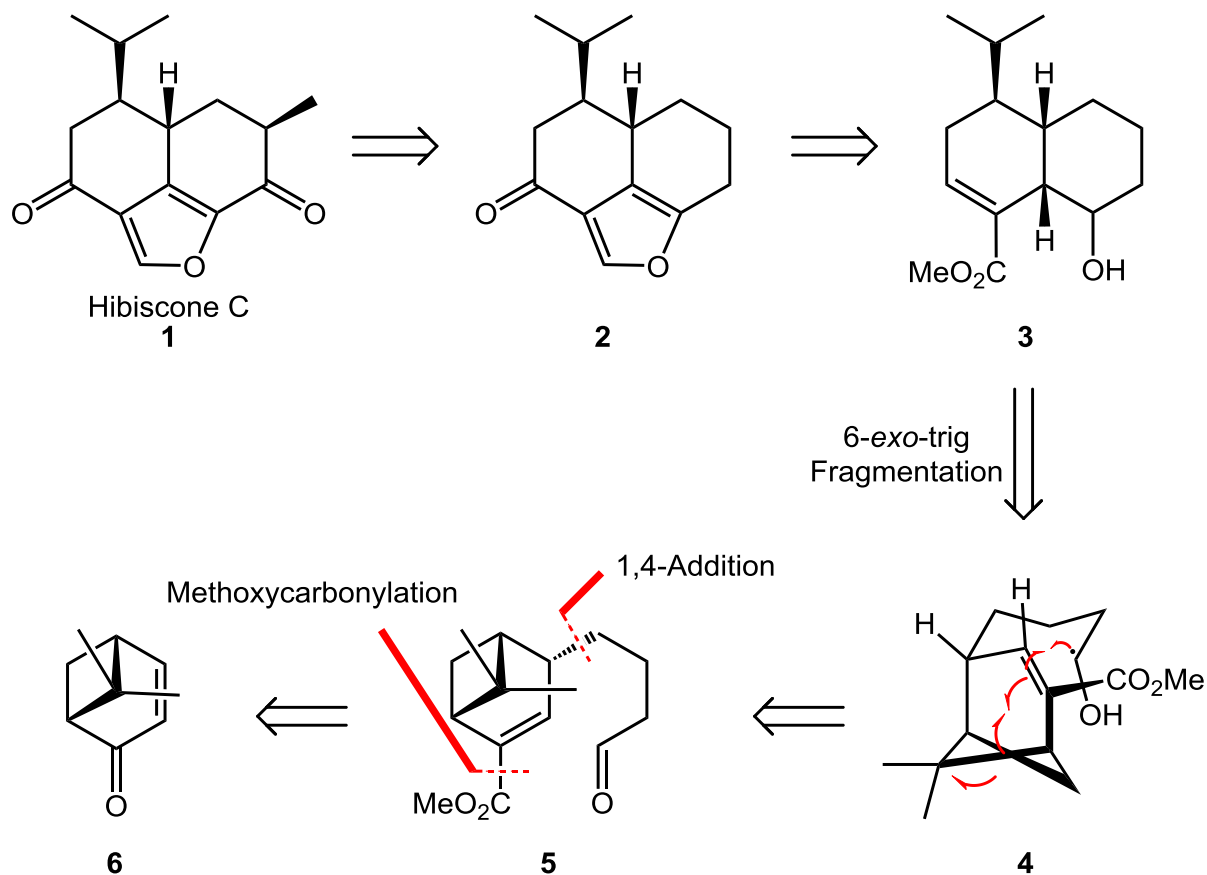


(-)-Hibiscone C

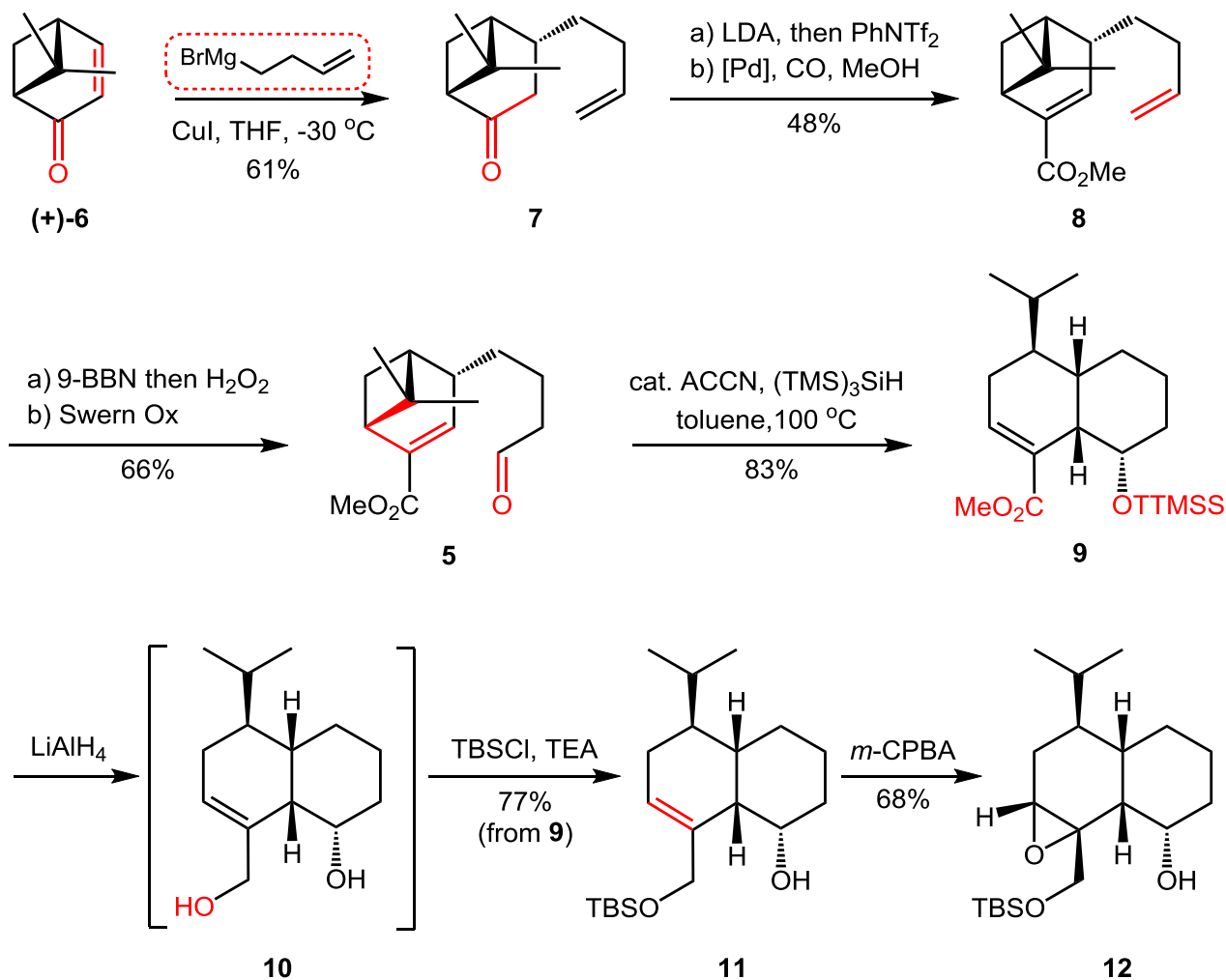


(±)-Lysergine

# Retrosynthetic Analysis of (-)-Hibiscone C

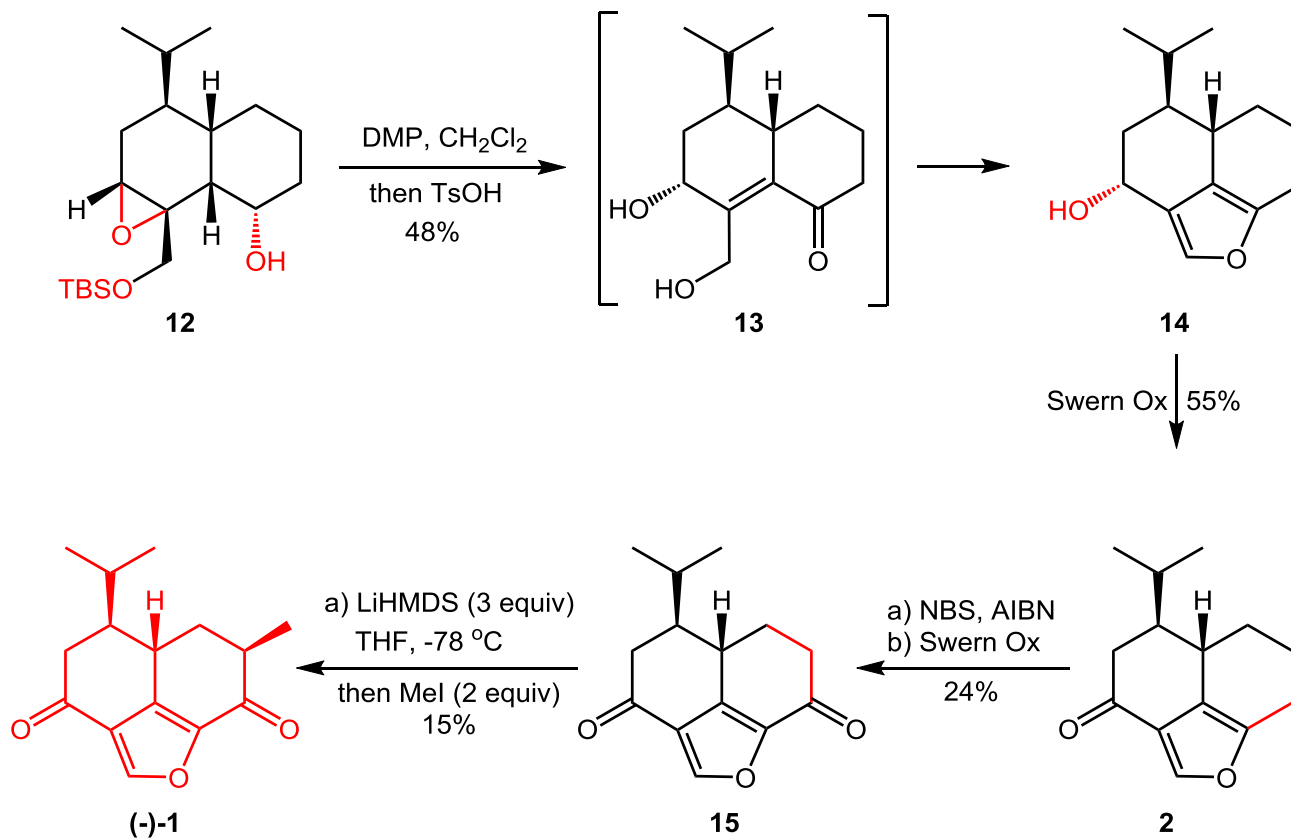


# Synthesis of Functionalized *cis*-Decalin 12

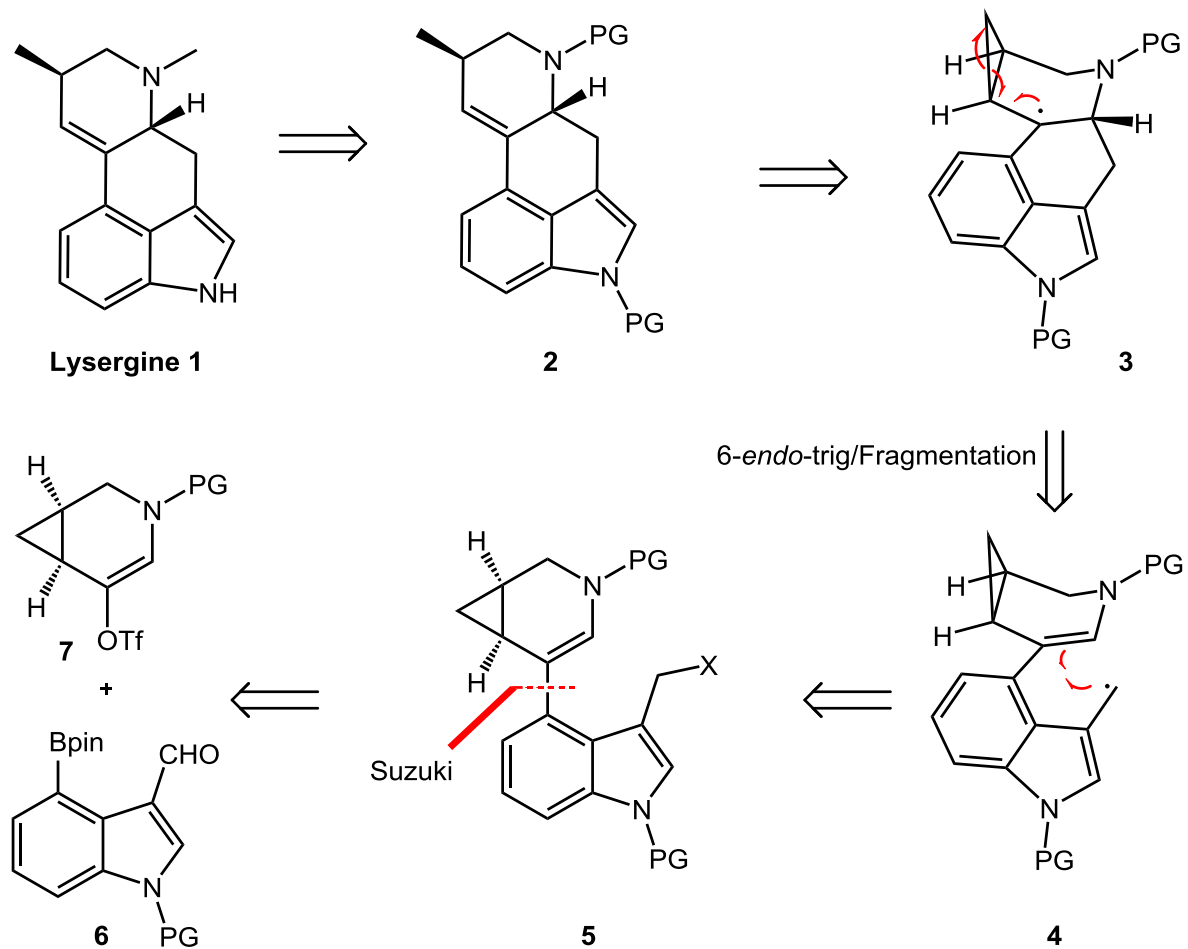




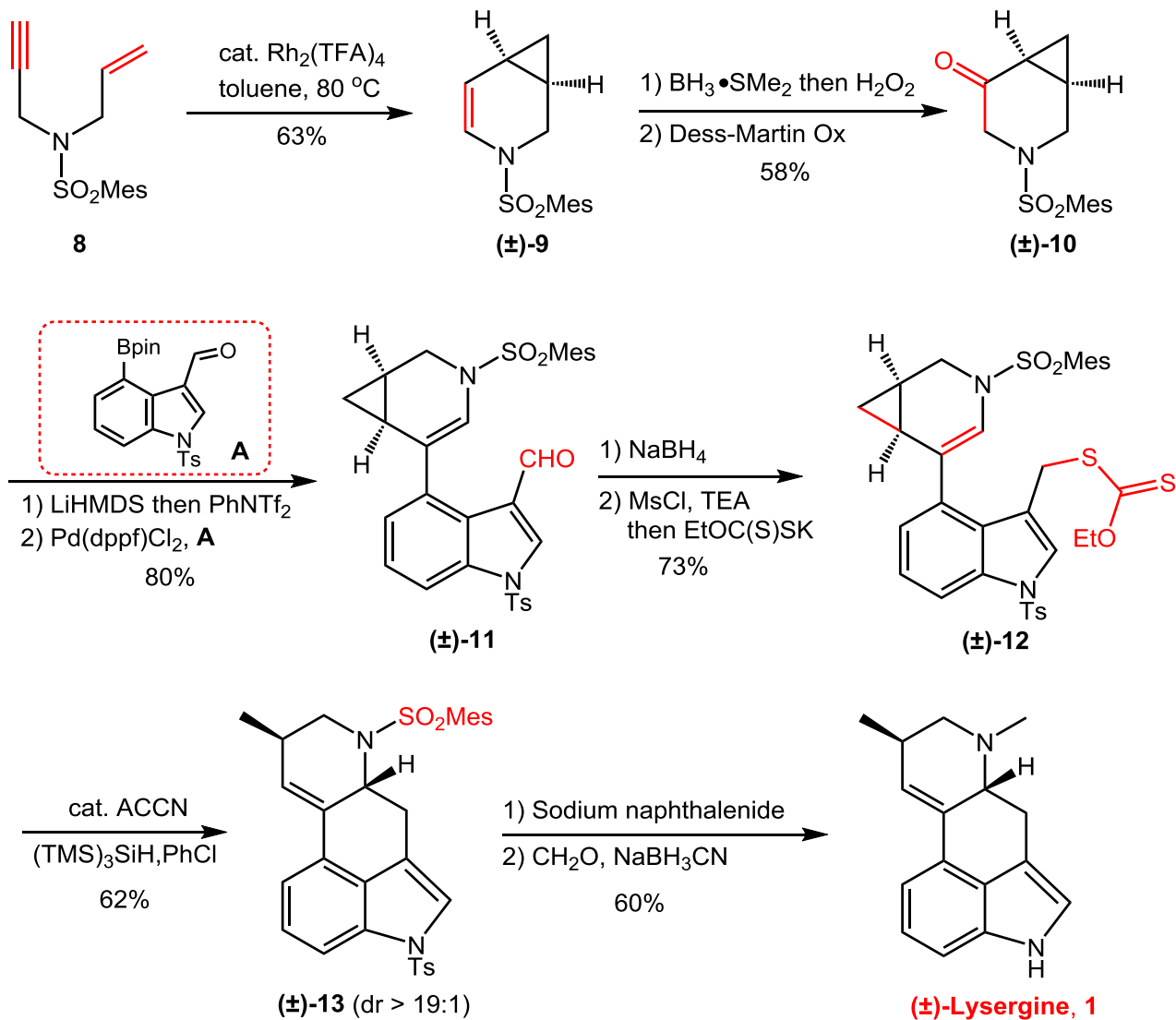
# Synthesis of (-)-Hibiscone C



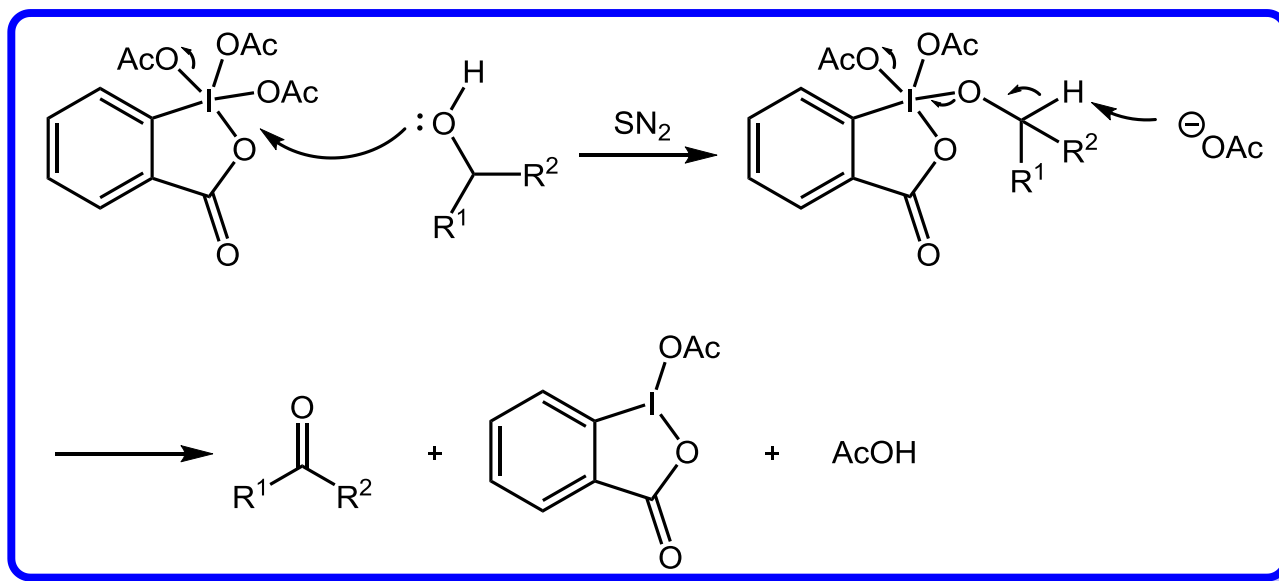
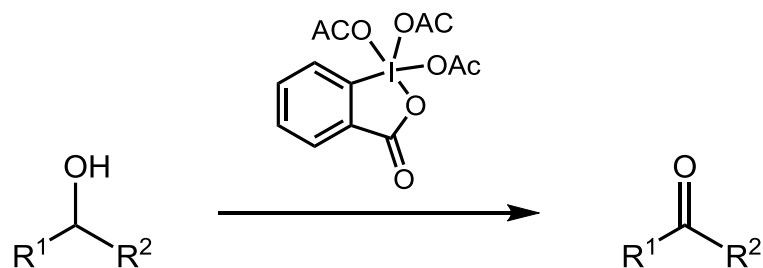
# Retrosynthetic Analysis of Lysergine



# Synthesis of Lysergine

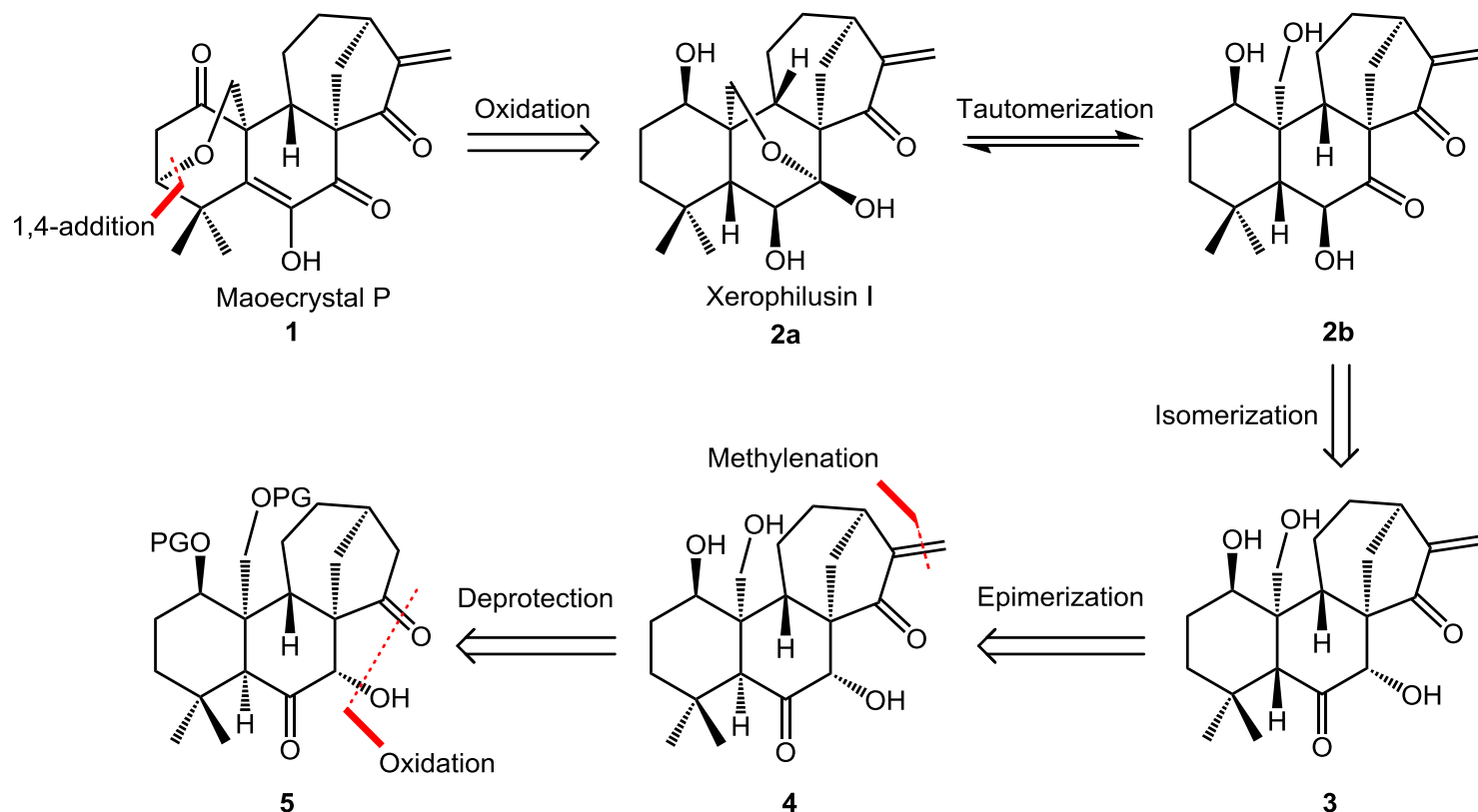


# Dess-Martin Periodinane Oxidation



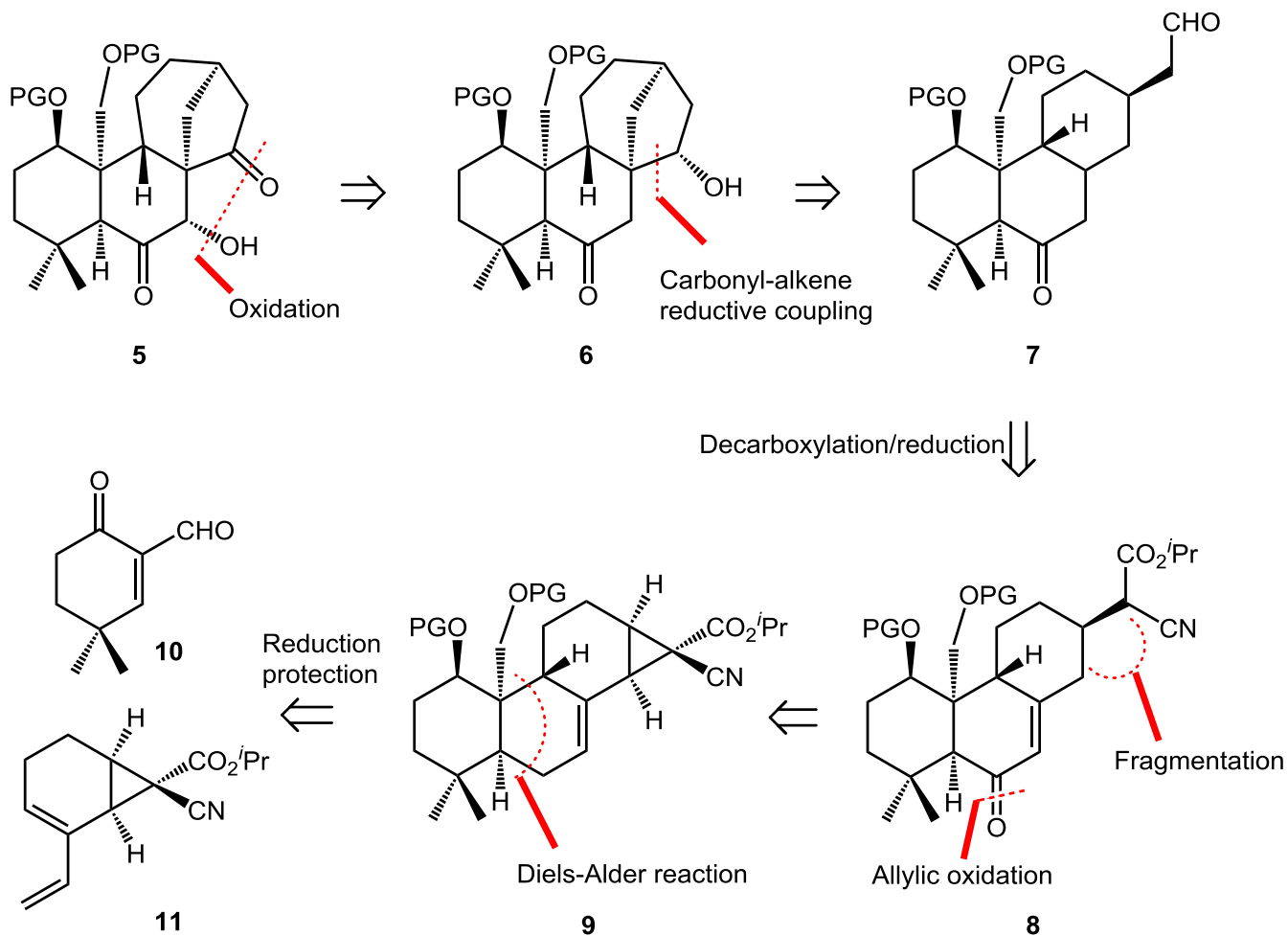
Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

# Retrosynthetic Analysis of Maoecrystal P

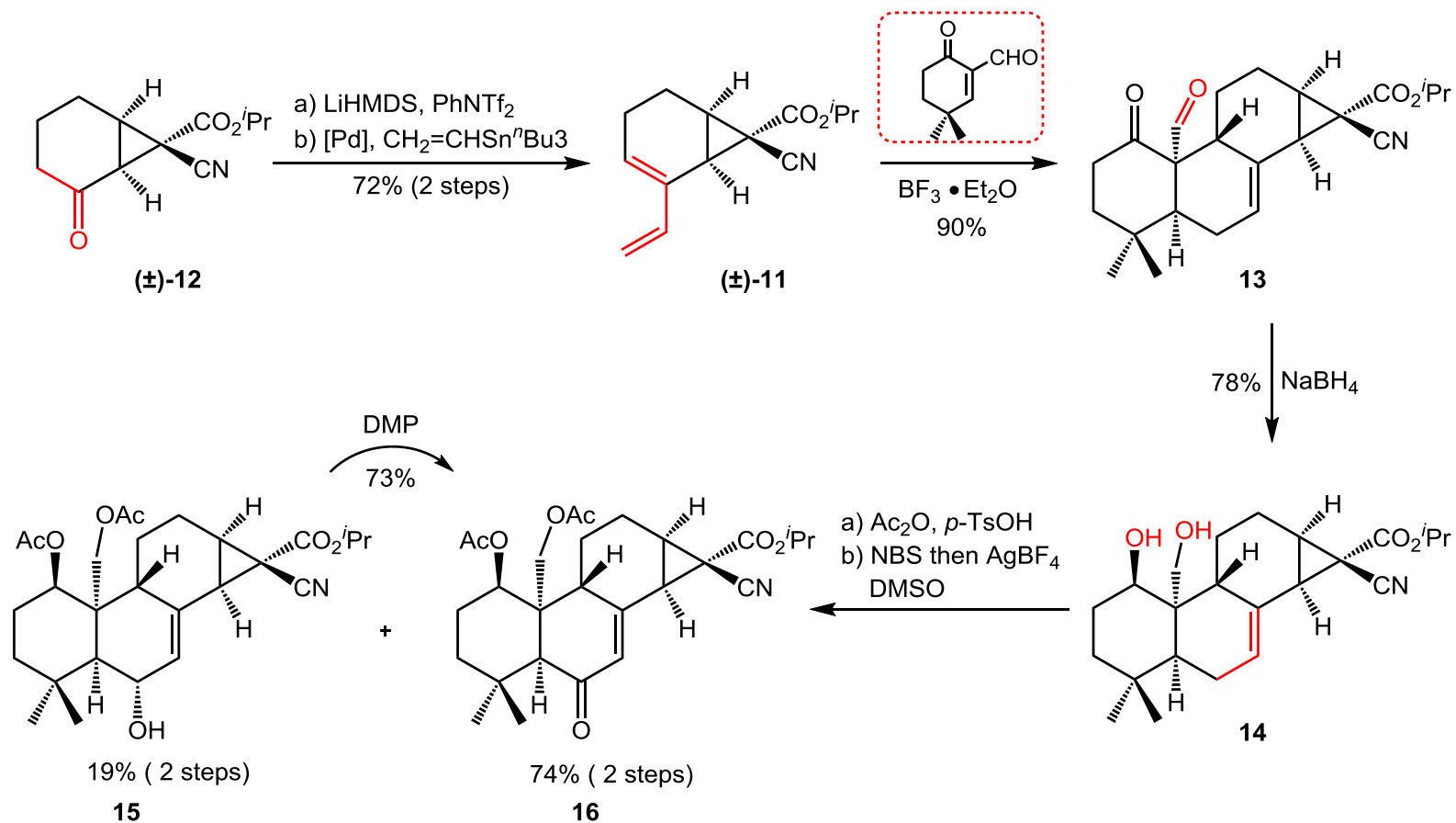


Su, F.; Lu, Y.; Kong, L.; Liu, J.; Luo, T. *Angew. Chem. Int. Ed.* **2018**, *57*, 760.

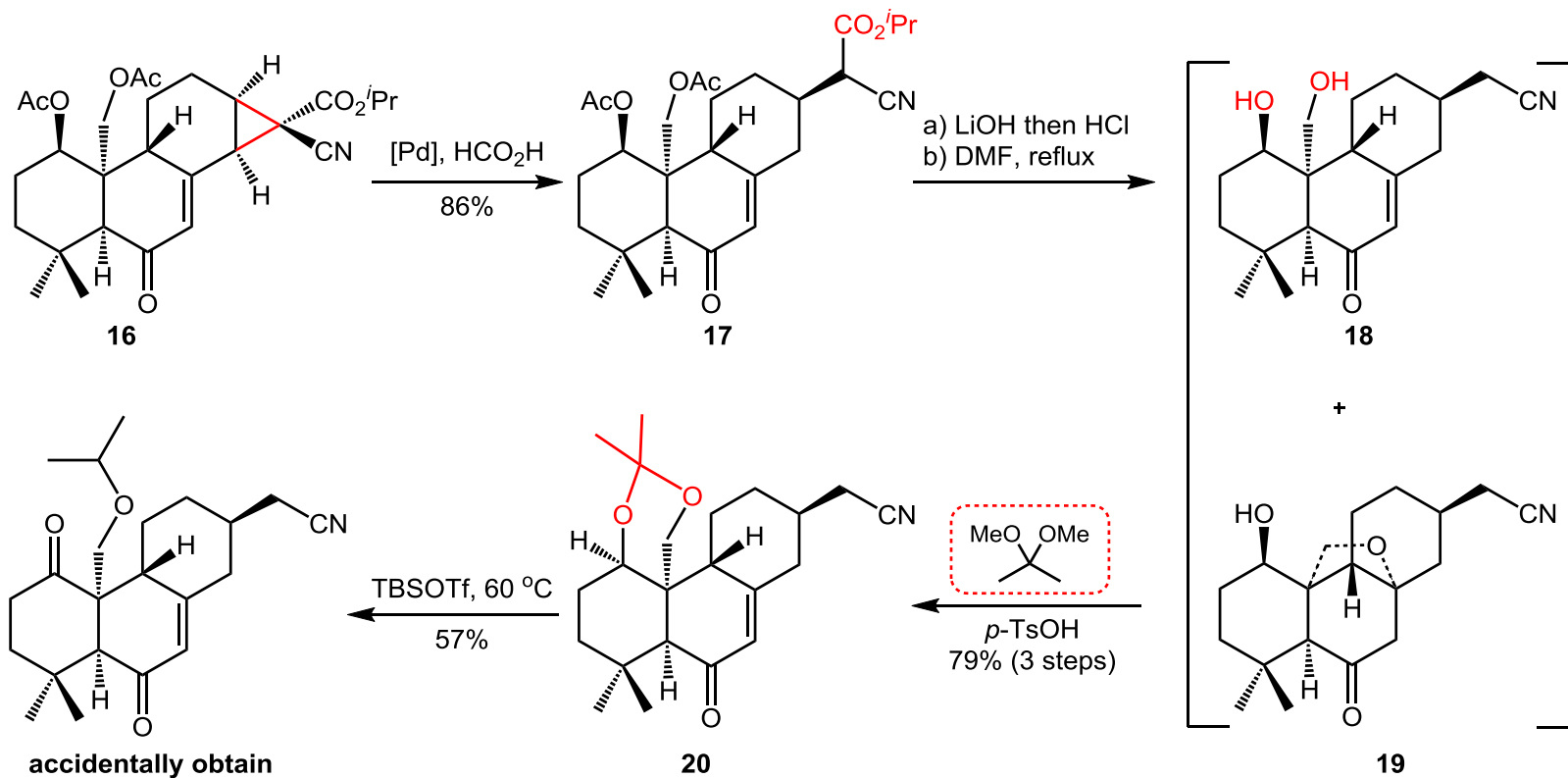
# Retrosynthetic Analysis of Maoecrystal P



# Synthesis of Maoecrystal P

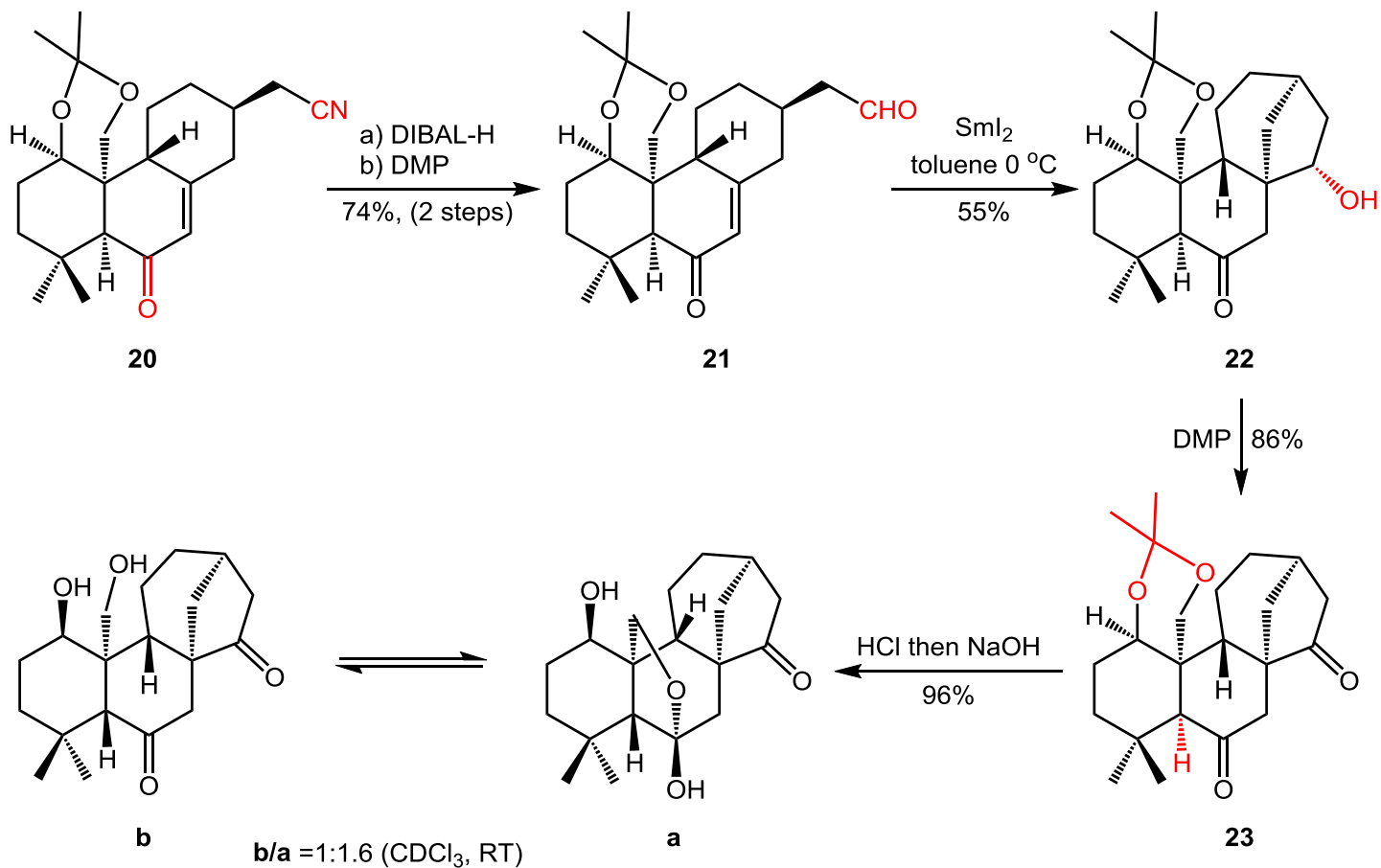


# Synthesis of Maoecrystal P

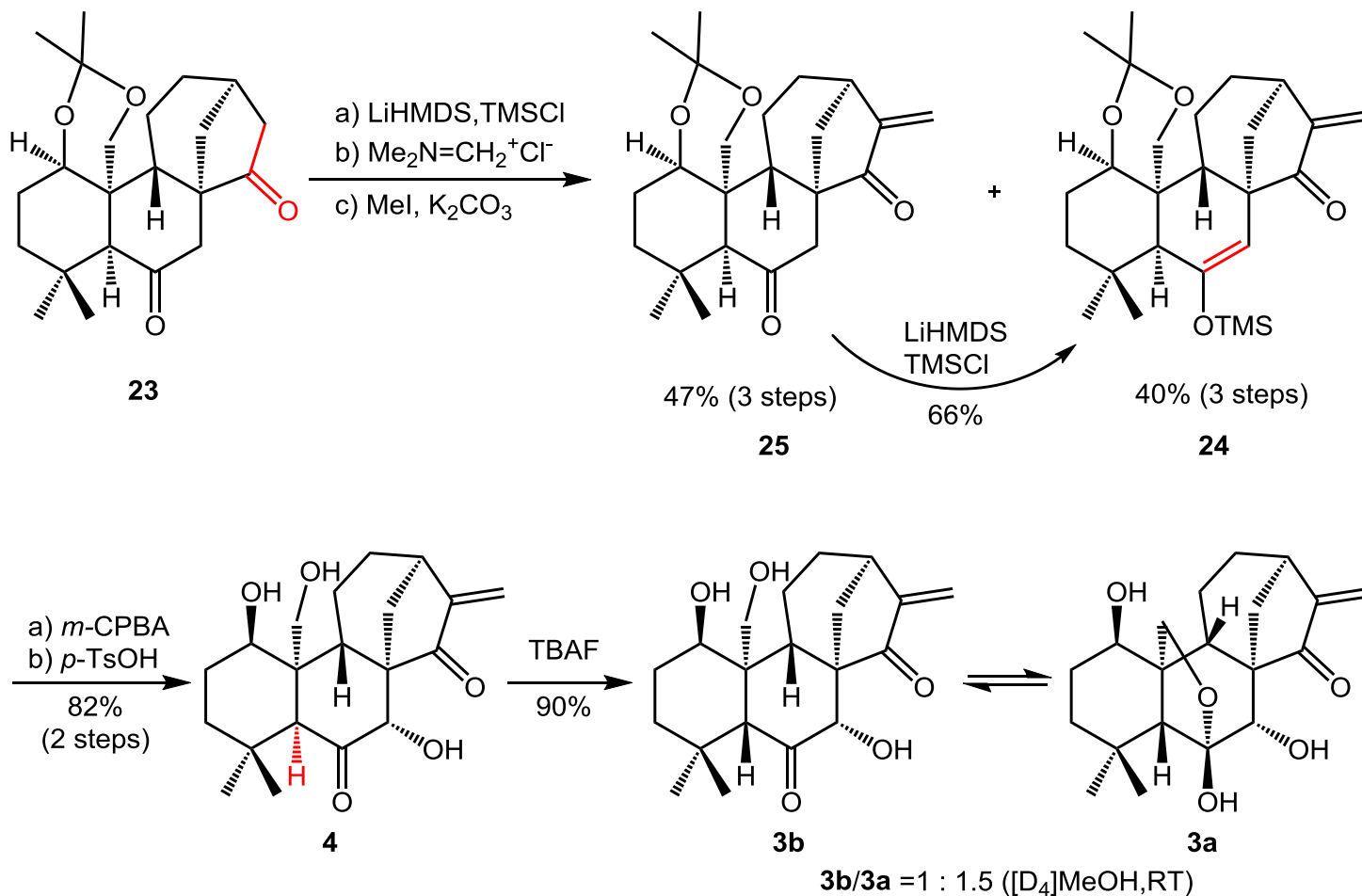




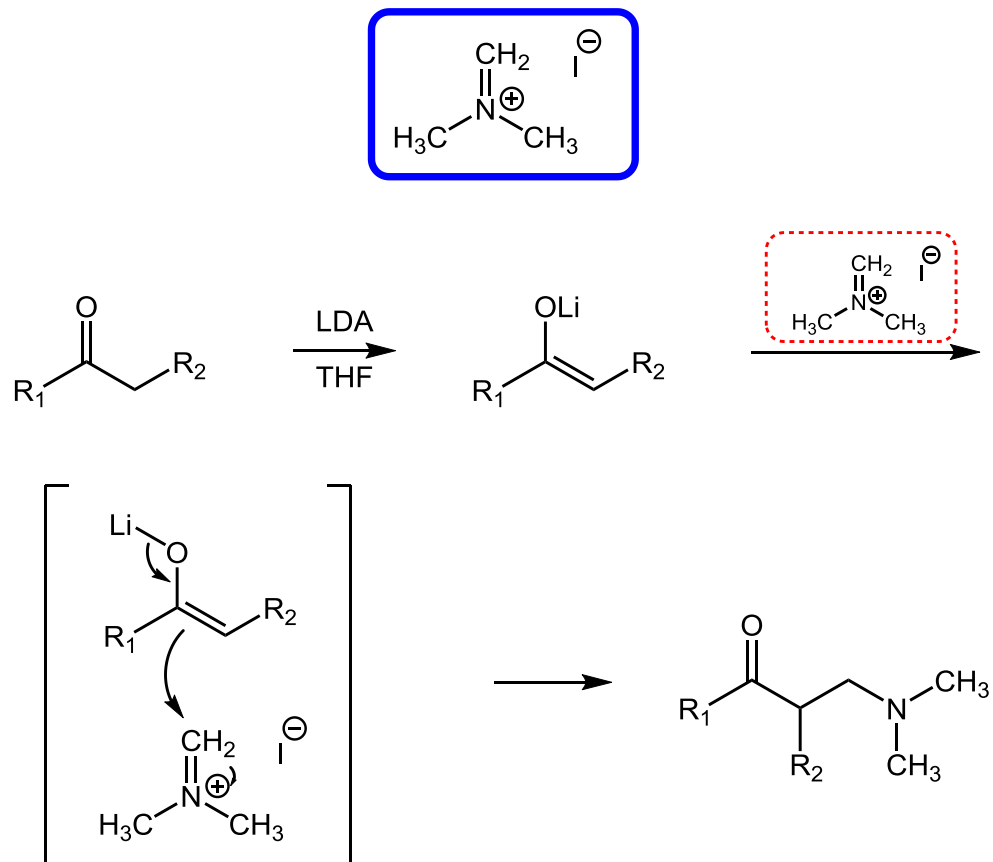
# Synthesis of Maoecrystal P



# Synthesis of Maoecrystal P

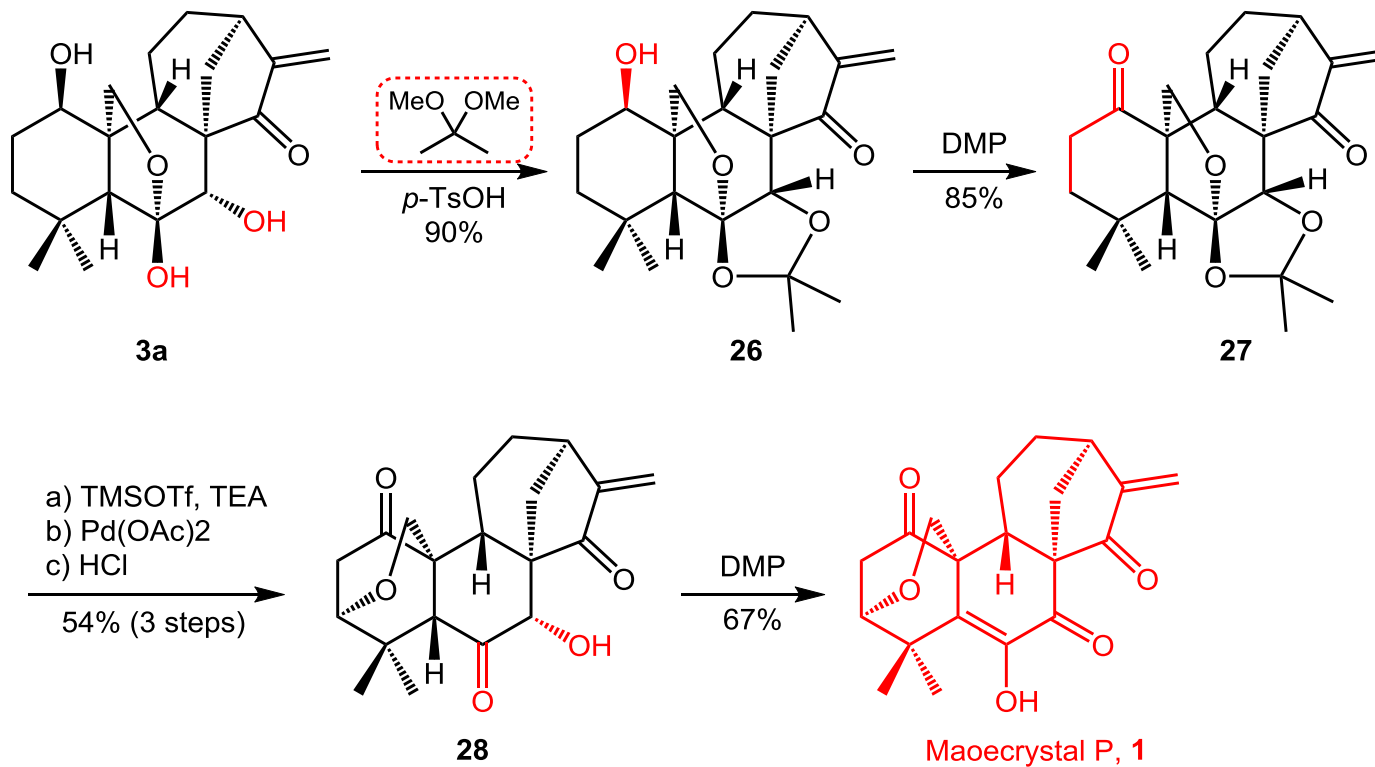


# Eschenmoser's salt



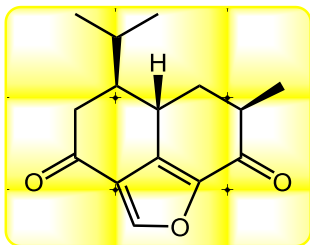
Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

# Synthesis of Maoecrystal P

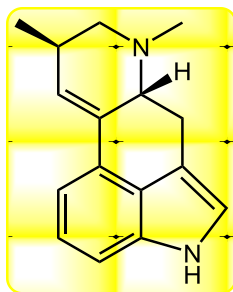


# Summary

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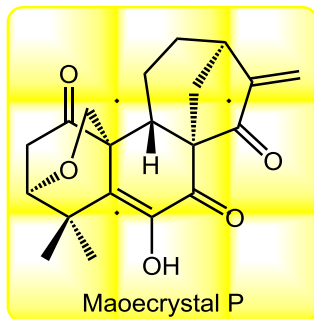


(-)-Hibiscone C



(±)-Lysergine

- (-)-Hibiscone C, 15 Steps, 0.08% yield;
- (±)-Lysergine, 10 steps, 7.93% yield;
- Radical cyclization/fragmentation strategy.



- 27 Steps, 1.15% overall yield;
- The first total synthesis of Maoecrystal P;
- The unique cyclopropyl ring;
- Intermolecular Diels-Alder reaction;
- Regioselective allylic oxidation.

# The First Paragraph

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The *ent*-kaurene diterpenoids comprise over 600 naturally occurring small molecules biosynthetically related to *ent*-kaurene. A wide range of biological activities together with intriguing structures resulting from dense functionalization and varied oxidation patterns have piqued tremendous interest in this family of natural products. Among these compounds, maoecrystal P has attracted our particular attention, because it has shown promising cytotoxicity against human tumor cells. Owing to the Michael acceptor reactivity of the  $\alpha$ -methylene cyclopentanone unit that is present in most bioactive *ent*-kauranoids, valuable insight into their mechanism of action has been gathered by the use of corresponding small-molecule probes. As part of our continuing interest in compounds that can form covalent bonds with their protein targets, we describe herein the first total synthesis of maoecrystal P.

# The Last Paragraph

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In summary, we have developed a synthesis of maoecrystal P with 27 steps in the longest linear sequence from commercially available 2-bromocyclohex-2-one. Notably, the unique cyclopropyl ring in **13** facilitated 1) the regioselective preparation of the vinyl triflate intermediate; 2) a highly stereoselective intermolecular Diels–Alder reaction; 3) regioselective allylic oxidation; and 4) the reductive scission of the C14-C16 bond. This novel strategy has the potential to be applied for the preparation of other highly oxidized *ent*-kauranoids and their analogues for biological evaluation. For example, synthesized **2** and our intermediates with the *ent*-kaurene skeleton (**4**, **29**, **30**, and **31**) all significantly inhibit the growth of HCT116 tumor cells with IC50 values ranging from 1 to 5  $\mu\text{m}$ . Related investigations are ongoing in our laboratory and will be reported in due course.

# Acknowledgement

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***Thanks  
for your attention***



# Baldwin环化规则

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➤环的大小：

欲形成环的链上原子数目。

➤受进攻原子的杂化情况：

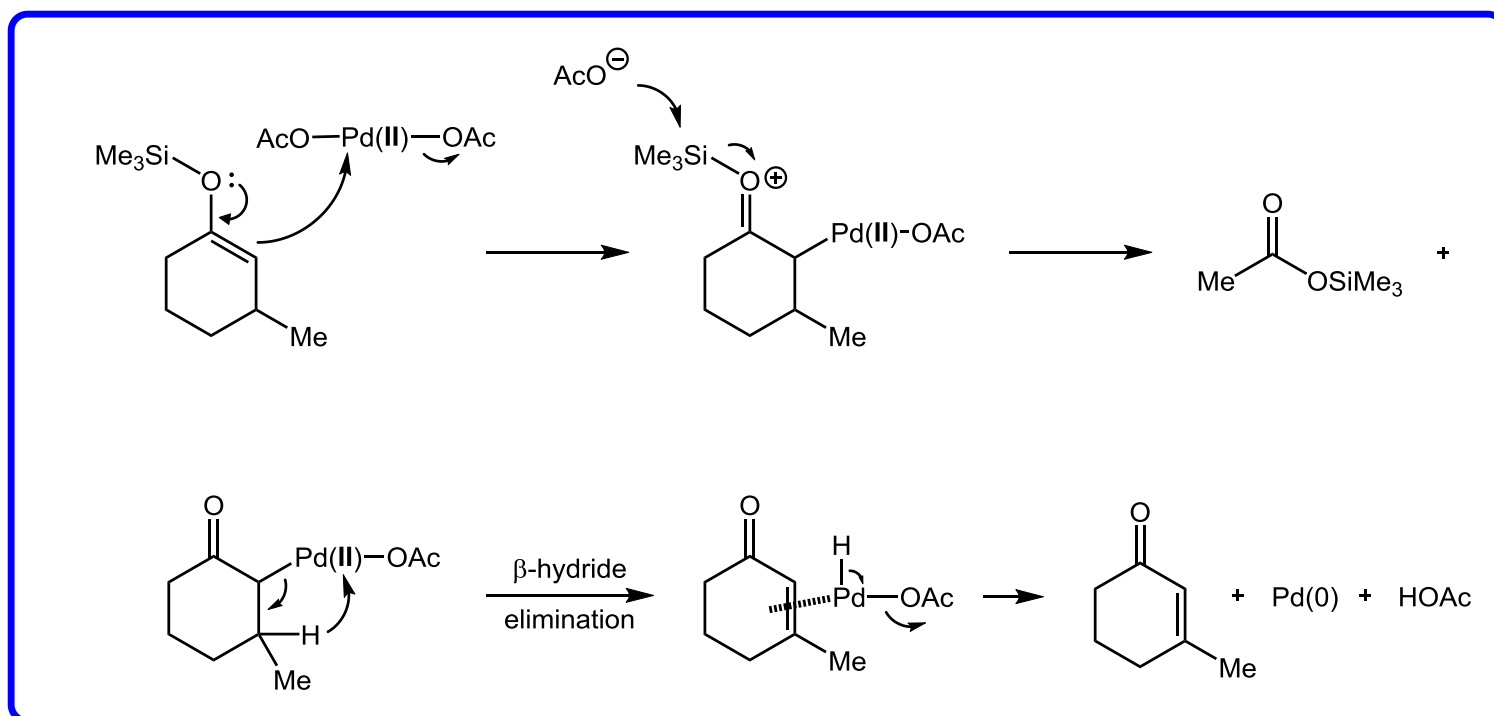
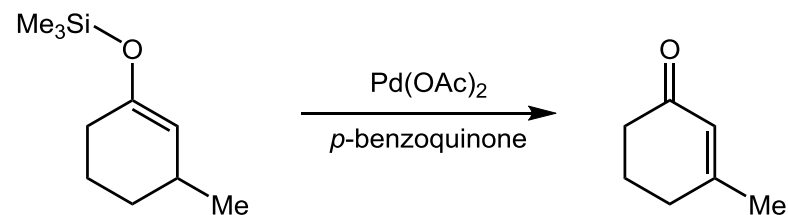
$Sp^3$ 杂化(tet)；  $Sp^2$ 杂化(trig)；  $Sp$ 杂化(dig)。

➤断键方式：

内式(*endo*) 电子向“环”内“流动”，形成较大的环；

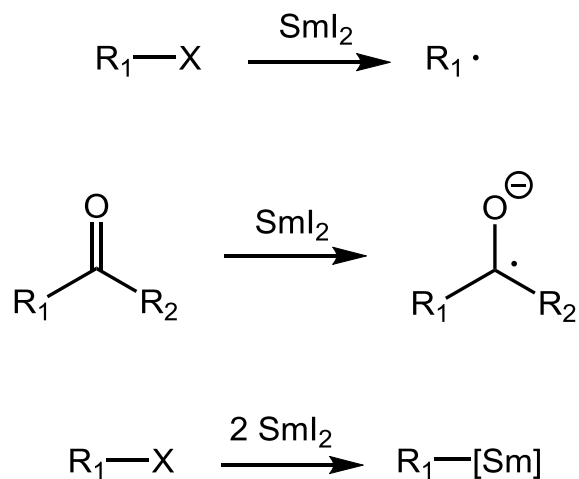
外式(*exo*) 电子向“环”外“流动”，形成较小的环。

# Saegusa Oxidation

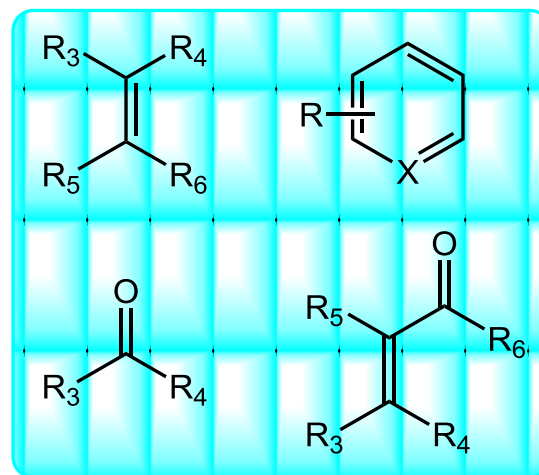


Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

# Samarium(II) Iodide



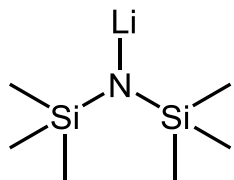
Acceptors



Szostak, M.; Fazakerley, N.; Parmar, D.; Procter, D. *Chem. Rev.* **2014**, *114*, 5959.

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LiHMDS



ACCN:

