Literature Report Ⅰ

Total Synthesis of Illisimonin A and Merrilactone A

Reporter: Sai-Nan Yin
Checker: Gao-Wei Wang
Date: 2023-11-13

Gong, X.; Huang, J.; Sun, X.; Chen, Z.; Yang, M.* *Angew. Chem. Int. Ed.* **2023**, *62*, e202306367

CV of Prof. Ming Yang

Research Fields:

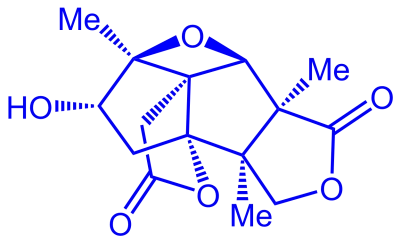
- Total Synthesis of Natural Products
- Organic Synthetic Methodology
- Medicinal Chemistry

Background:

- **2004-2008** B.S., Hubei University
- **2008-2013** Ph.D., Lanzhou University (Prof. Yong-Qiang Tu)
- **2013-2015** Postdoc., Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
- **2015-2018** Postdoc., The University of Chicago
- **2019-** Professor, College of Chemistry and Chemical Engineering, Lanzhou University

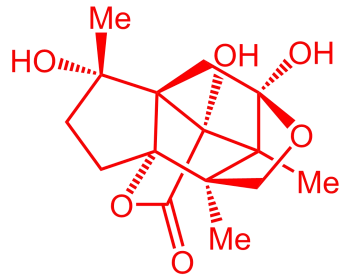
Contents

Introduction



Merrilactone A

Illicium Species Plants

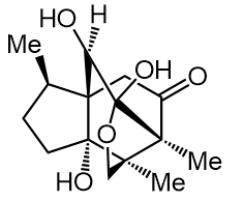


Illisimonin A

- Illicium sesquiterpenes were isolated from *Illicium* species plants (八角属植物);
- Some members of Illicium sesquiterpenes could be useful for the treatment of neurodegenerative diseases.

The Proposed Biosynthetic Pathway

allo-cedrane-type



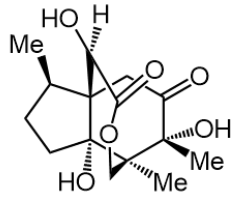
11-*O*-Debenzoyl Tashironin (9)

retro-Dieckmann condensation

& oxidation

oxidation & hemiketal formation

pseudoanisatin-subtype

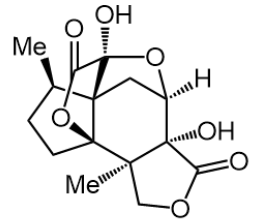


Parviflorolide (14)

reduction, lactonization

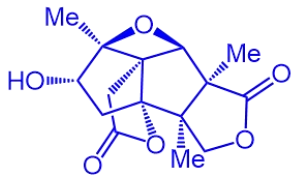
& oxidation

majucin-subtype

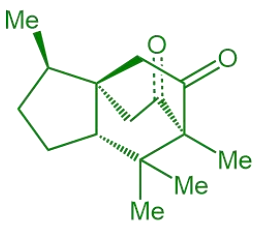


Jiadifenolide (16)

anislatone-type

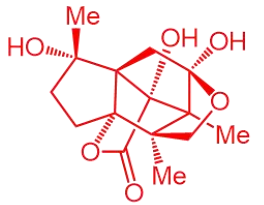


Merrilactone A (12)



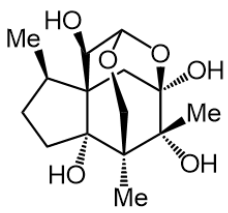
Common Intermediate (7)

illisimonane-type



Illisimonin A (19)

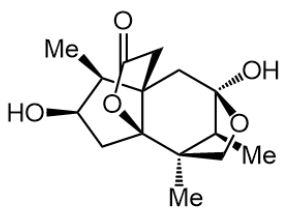
cycloparvifloralone-subtype



Cycloparvifloralone (24)

reduction

pseudomajucin-subtype

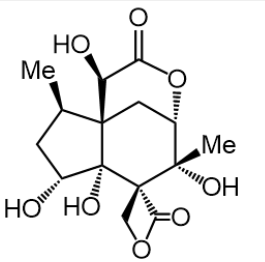


Pseudomajucin (23)

reduction, lactonization

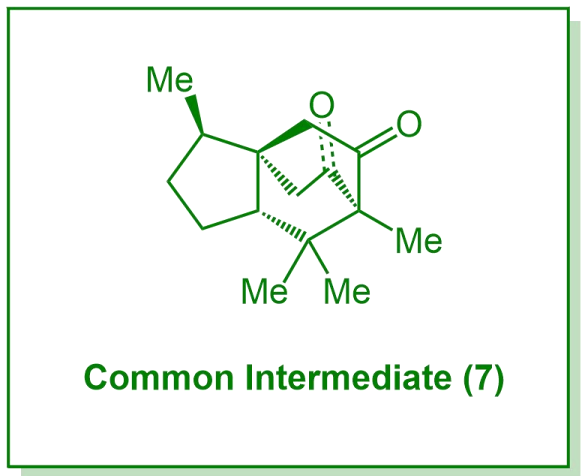
& oxidation

anisatin-subtype

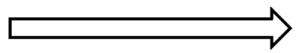


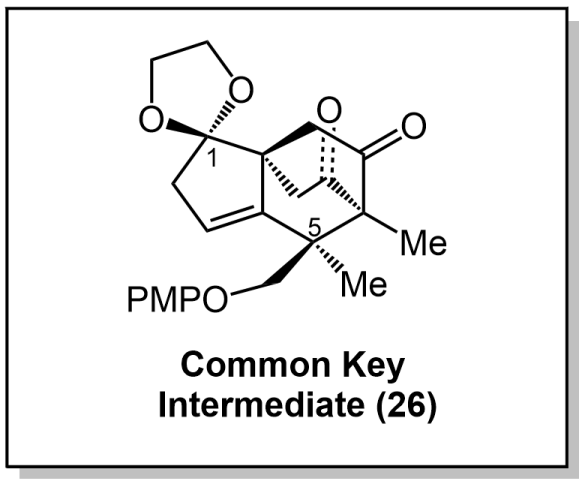
Anisatin (25)

The Common Key Intermediates



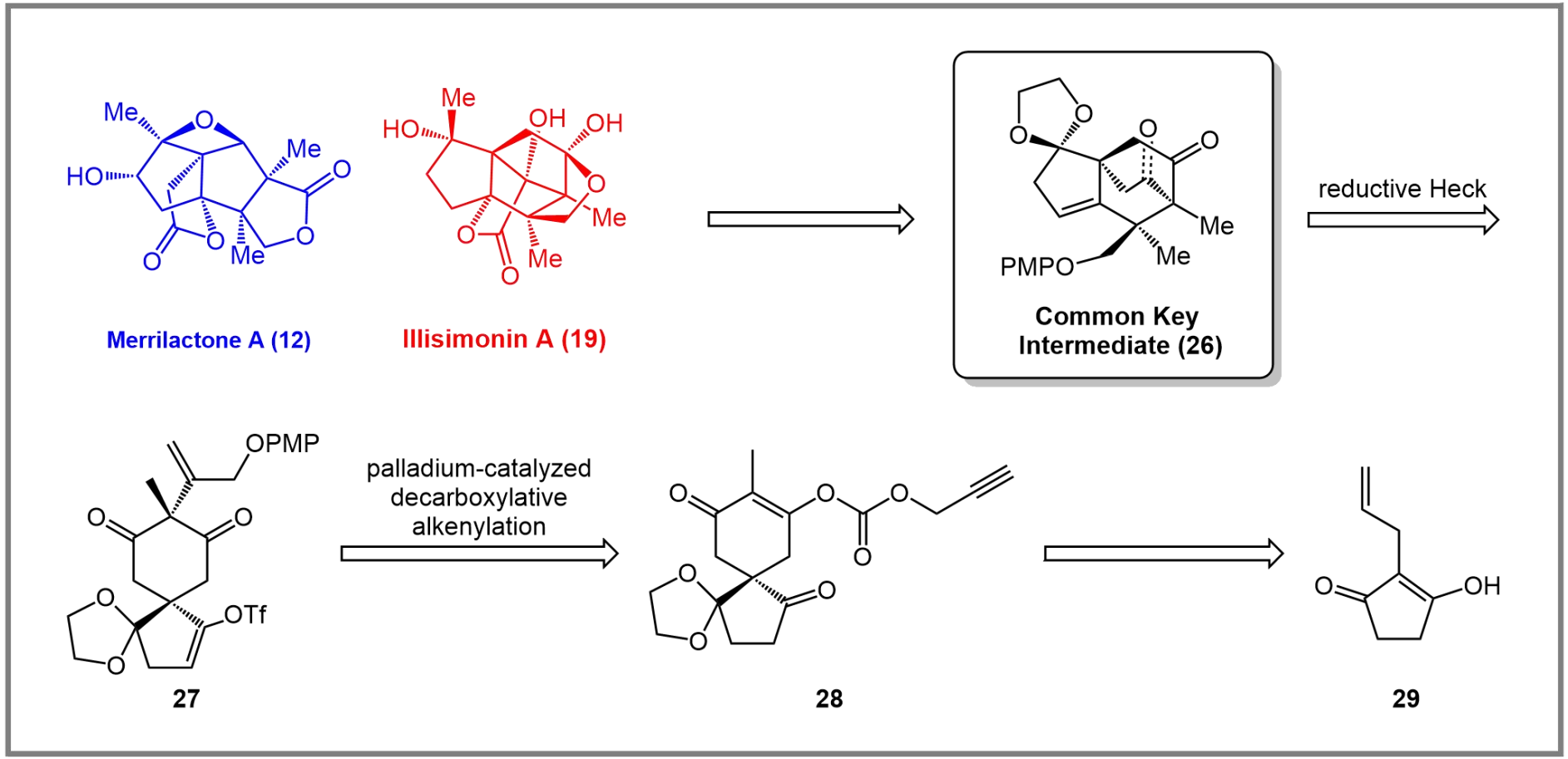
Common Intermediate (7)



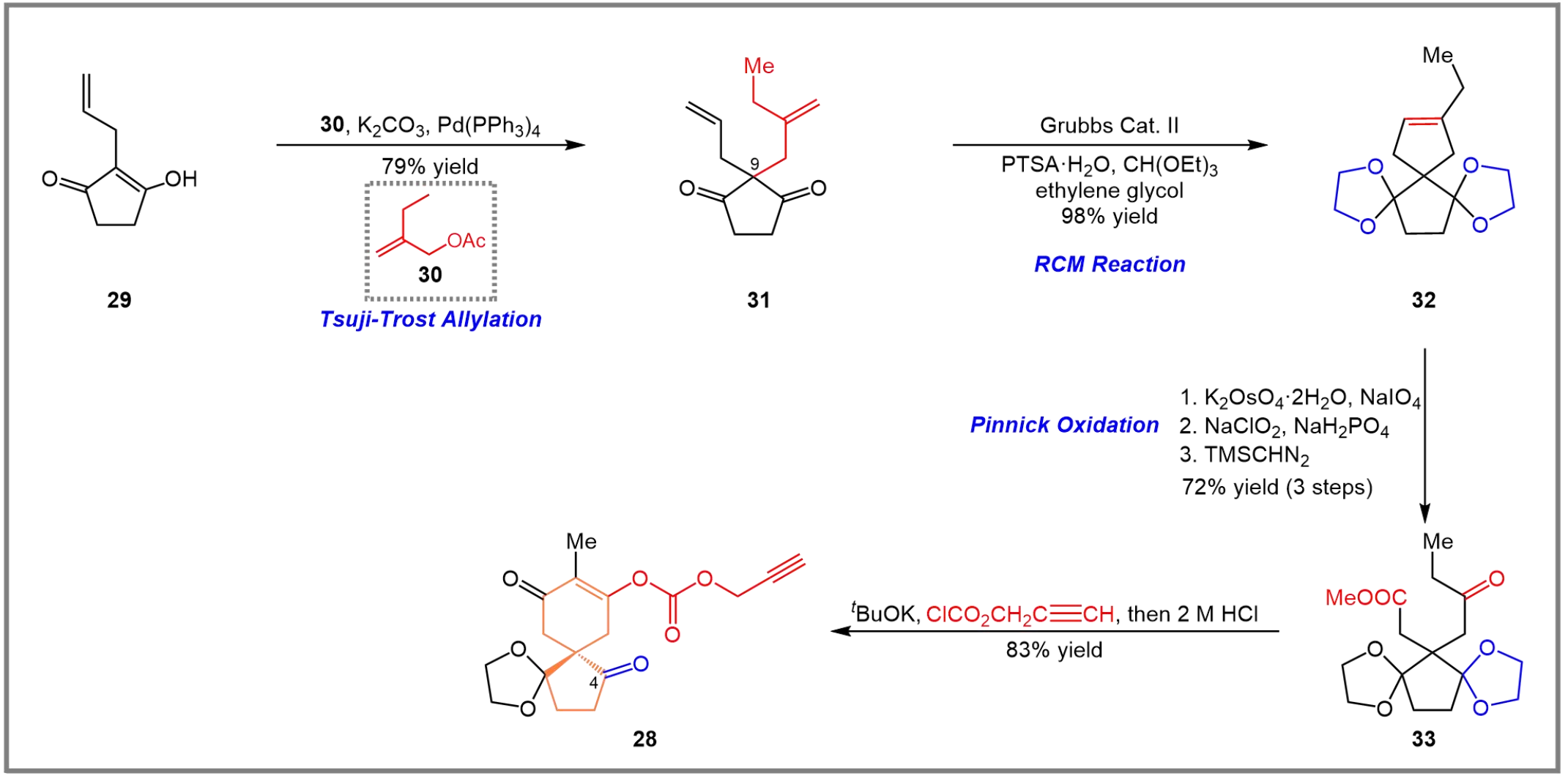


Common Key Intermediate (26)

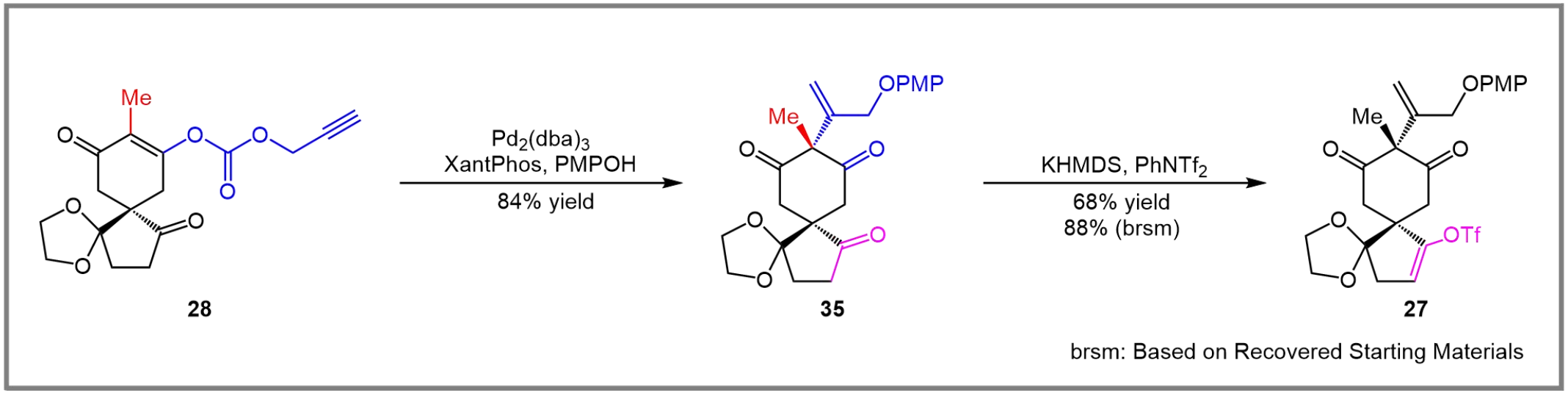
Retrosynthetic Strategy



Synthesis of the Spiro-[5.6]decane Skeleton of Compound 28



Synthesis of 1,3-Dicarbonyl Compound 27



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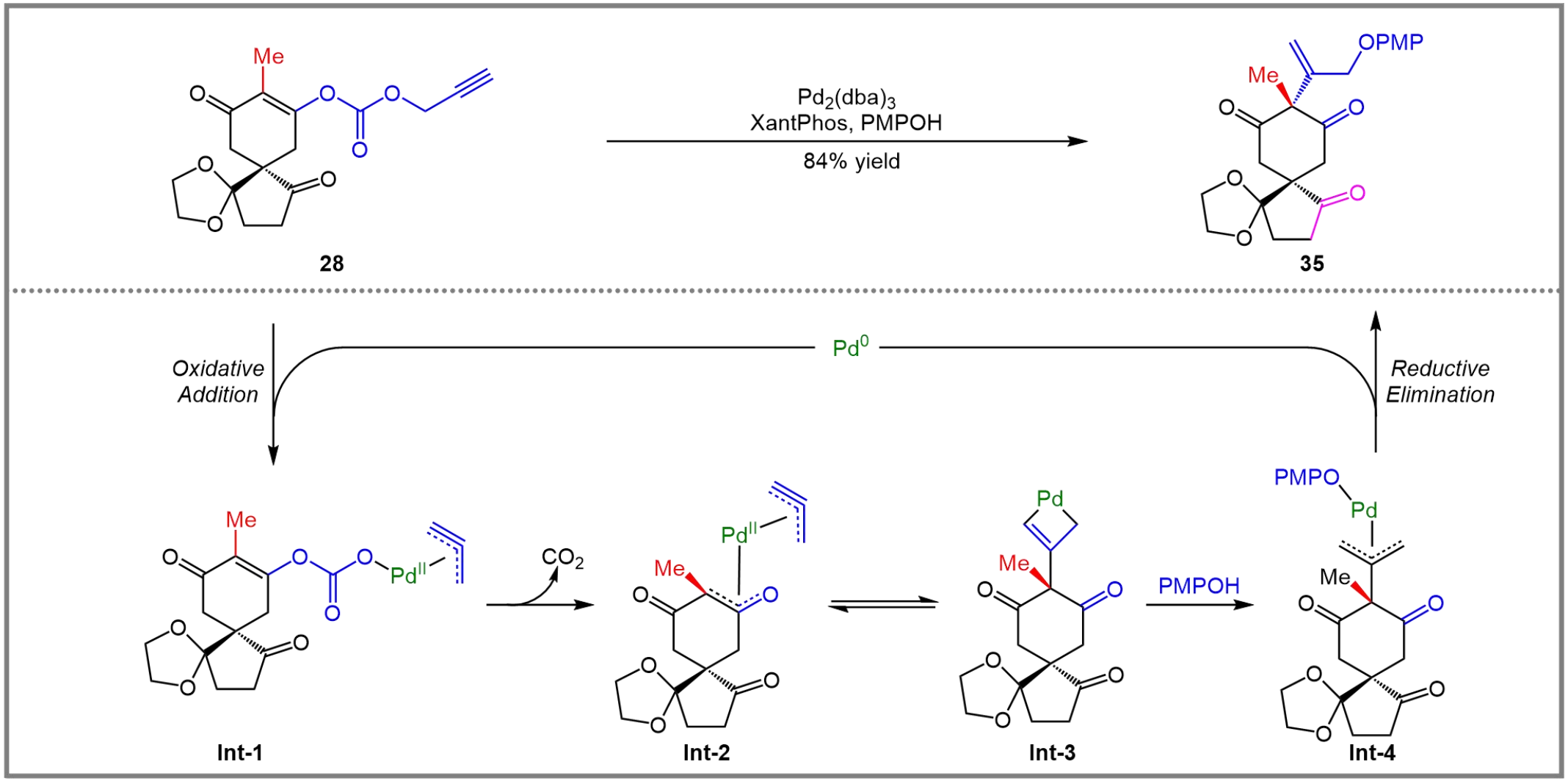

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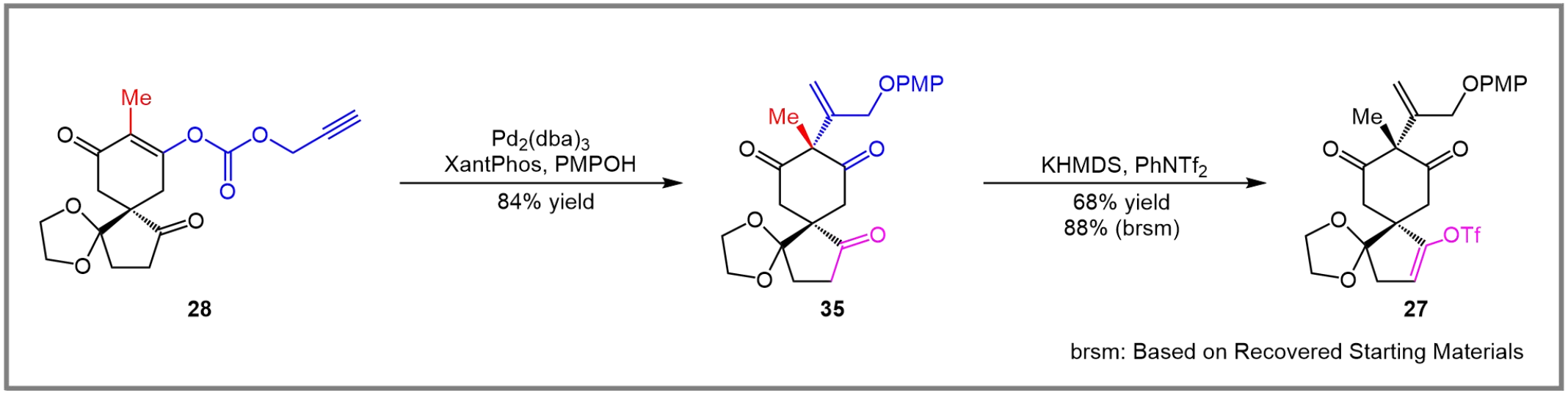
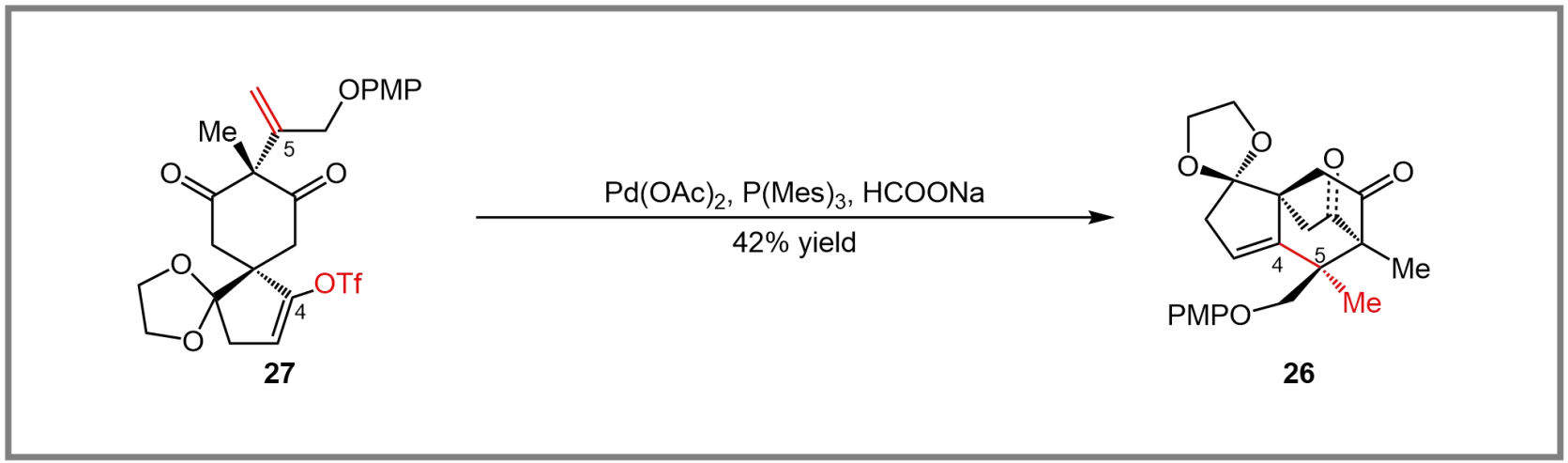
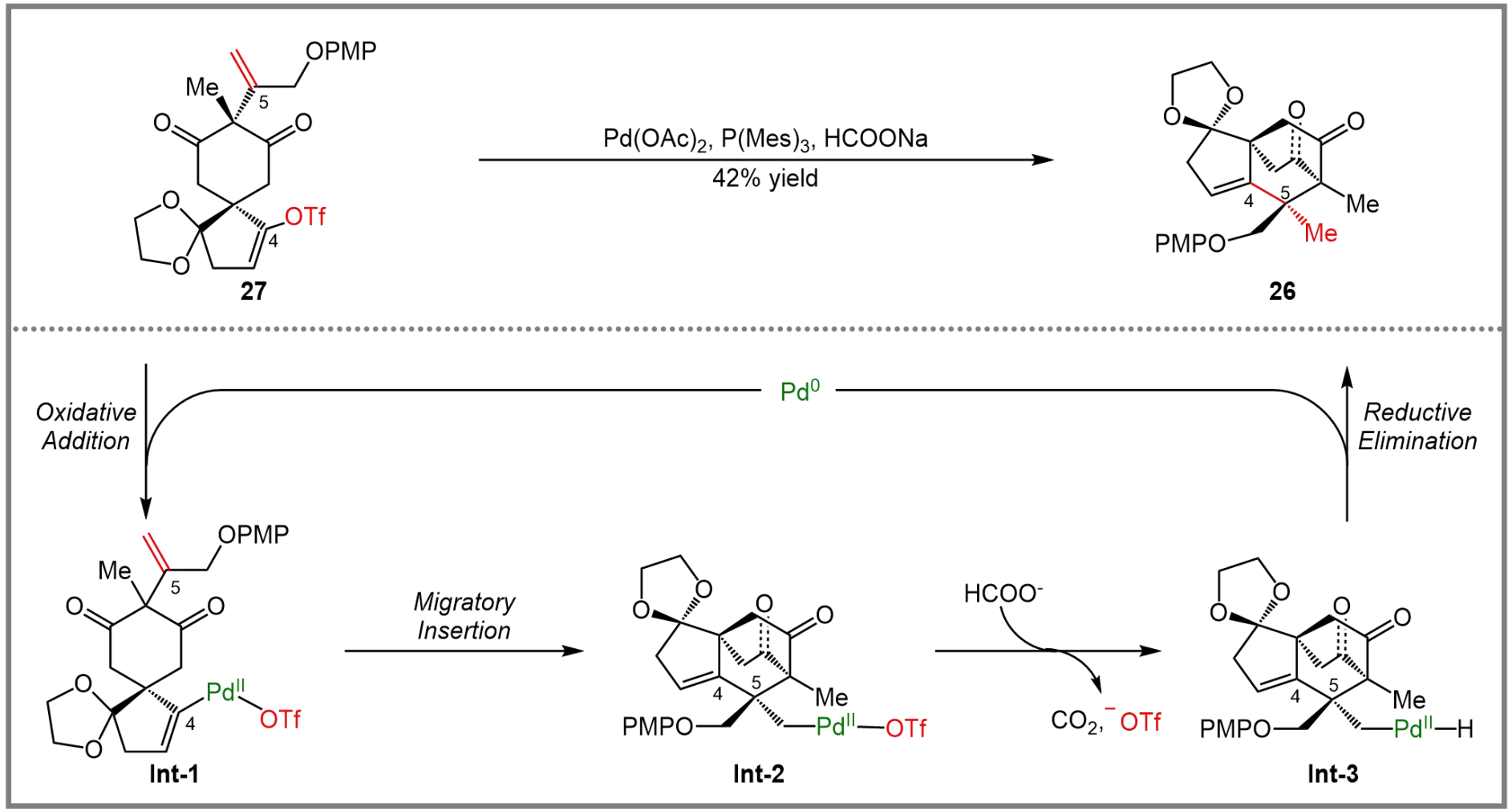


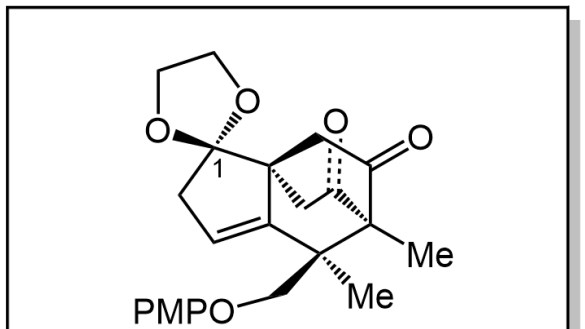
Synthesis of Key Intermediate 26



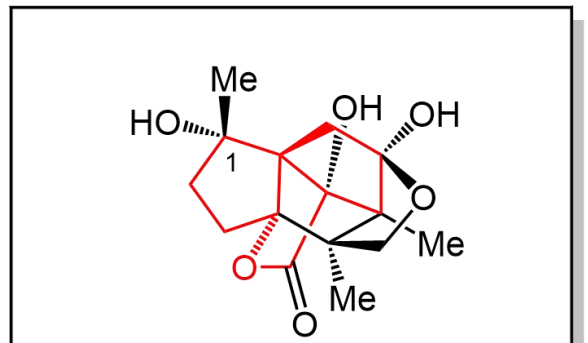
Synthesis of Key Intermediate 26



Synthesis of Illisimonin A

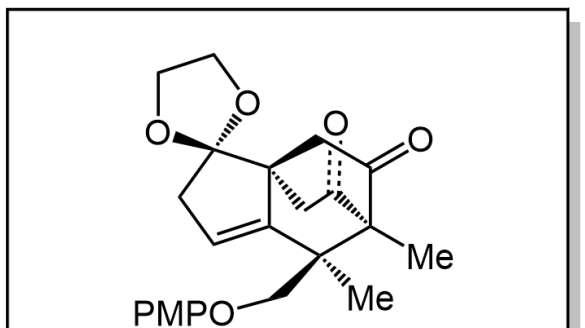


Common Key Intermediate (26)

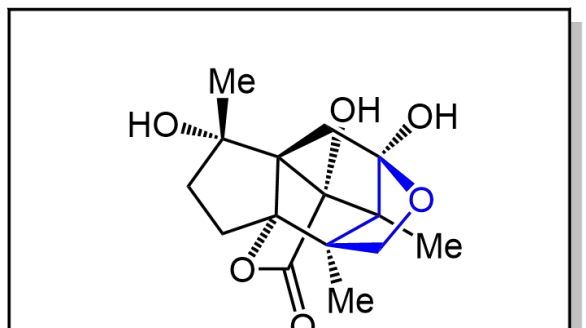


Illisimonin A (19)

Synthesis of Illisimonin A



Common Key Intermediate (26)



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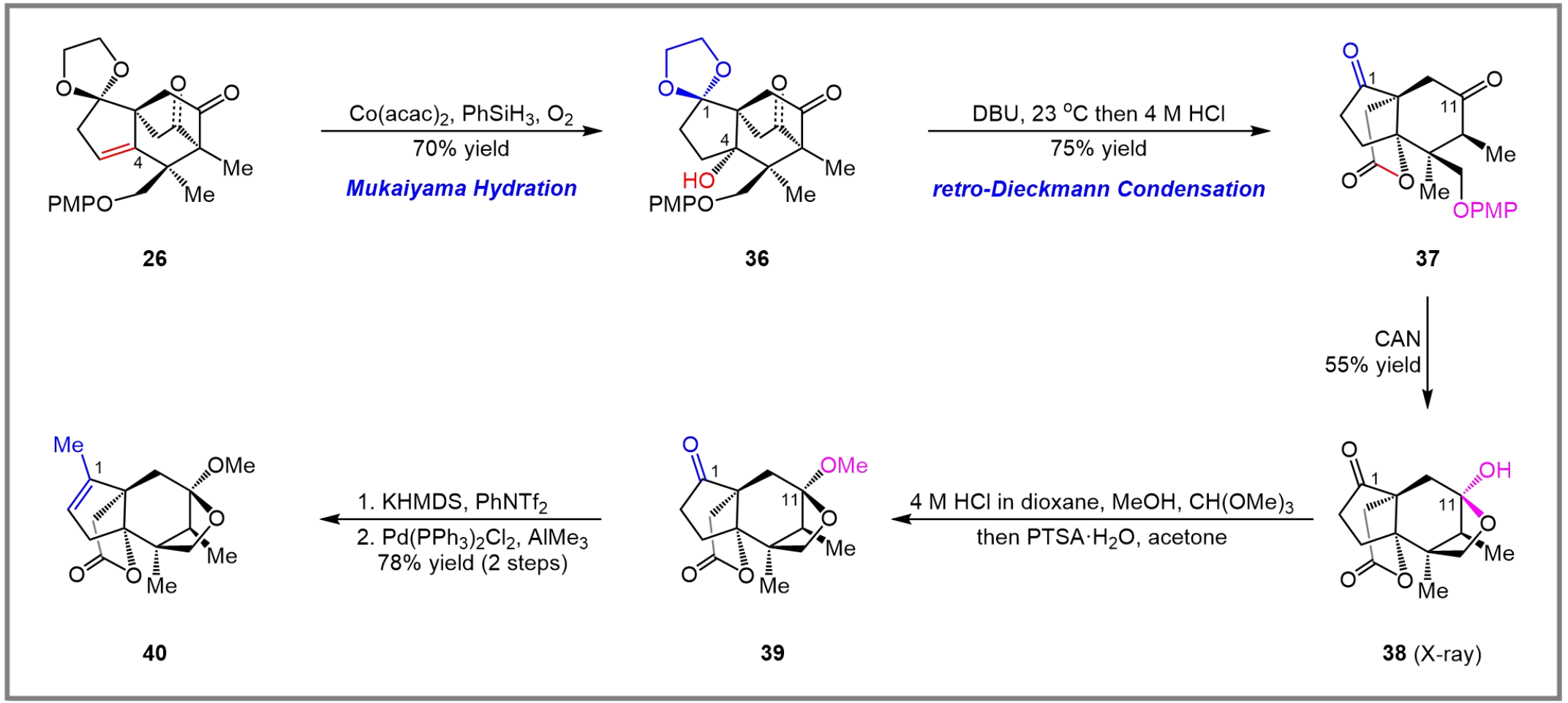

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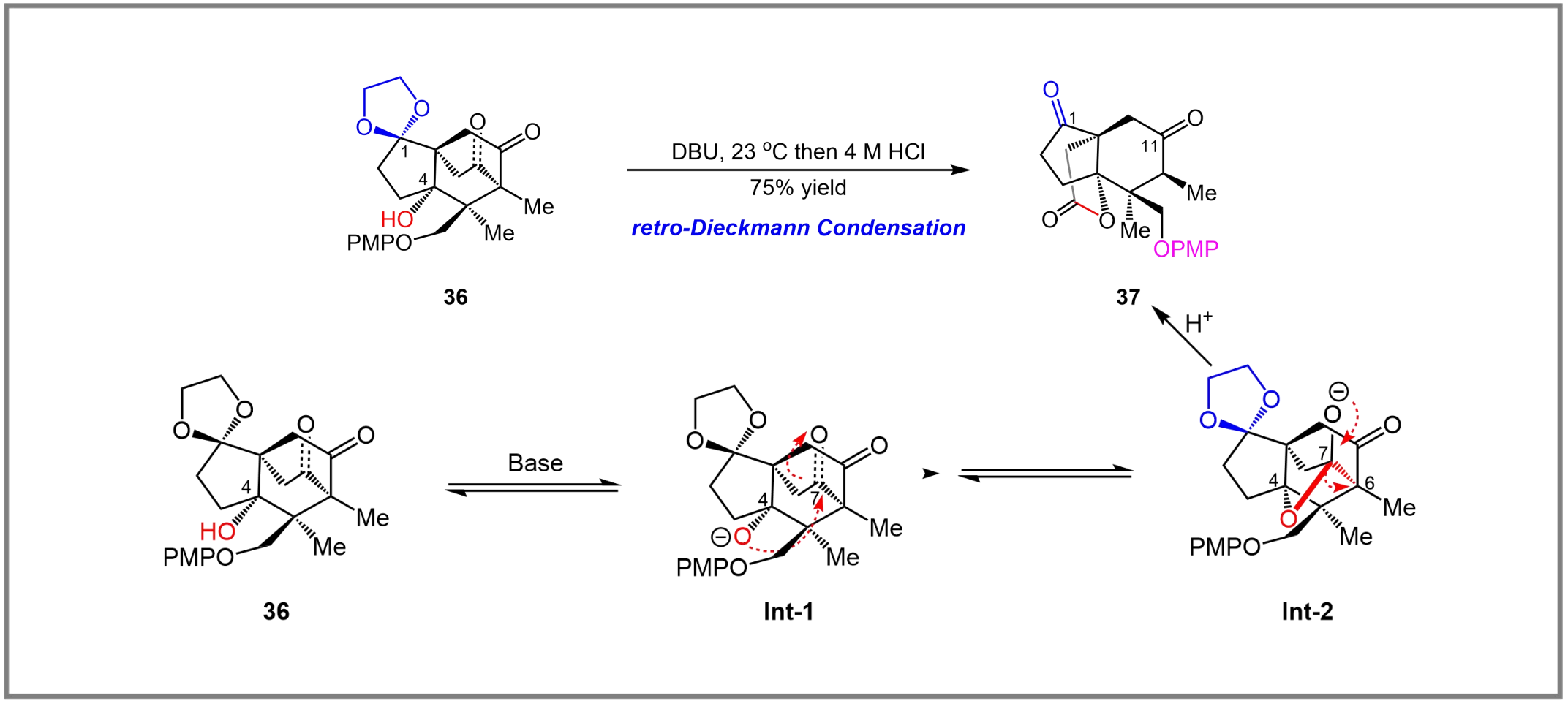

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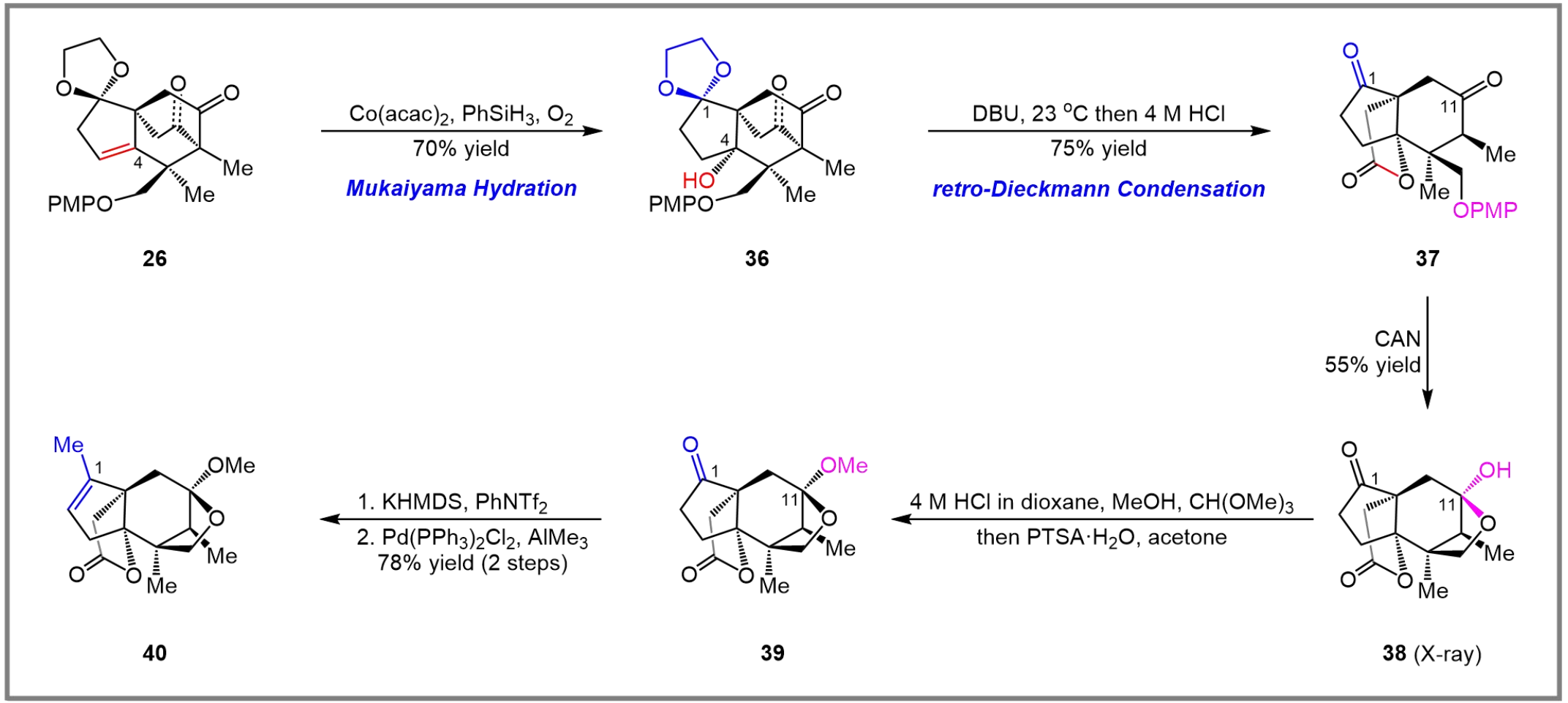

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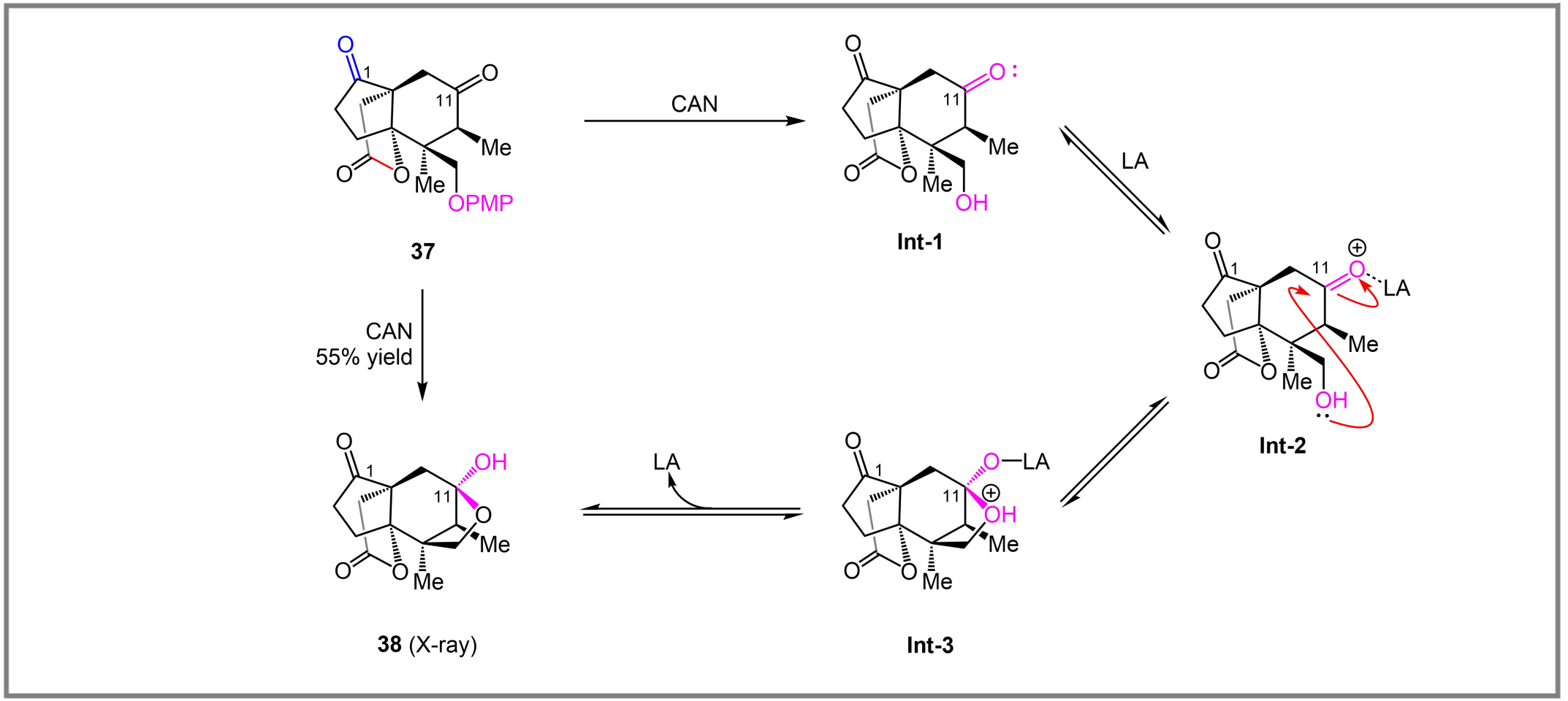

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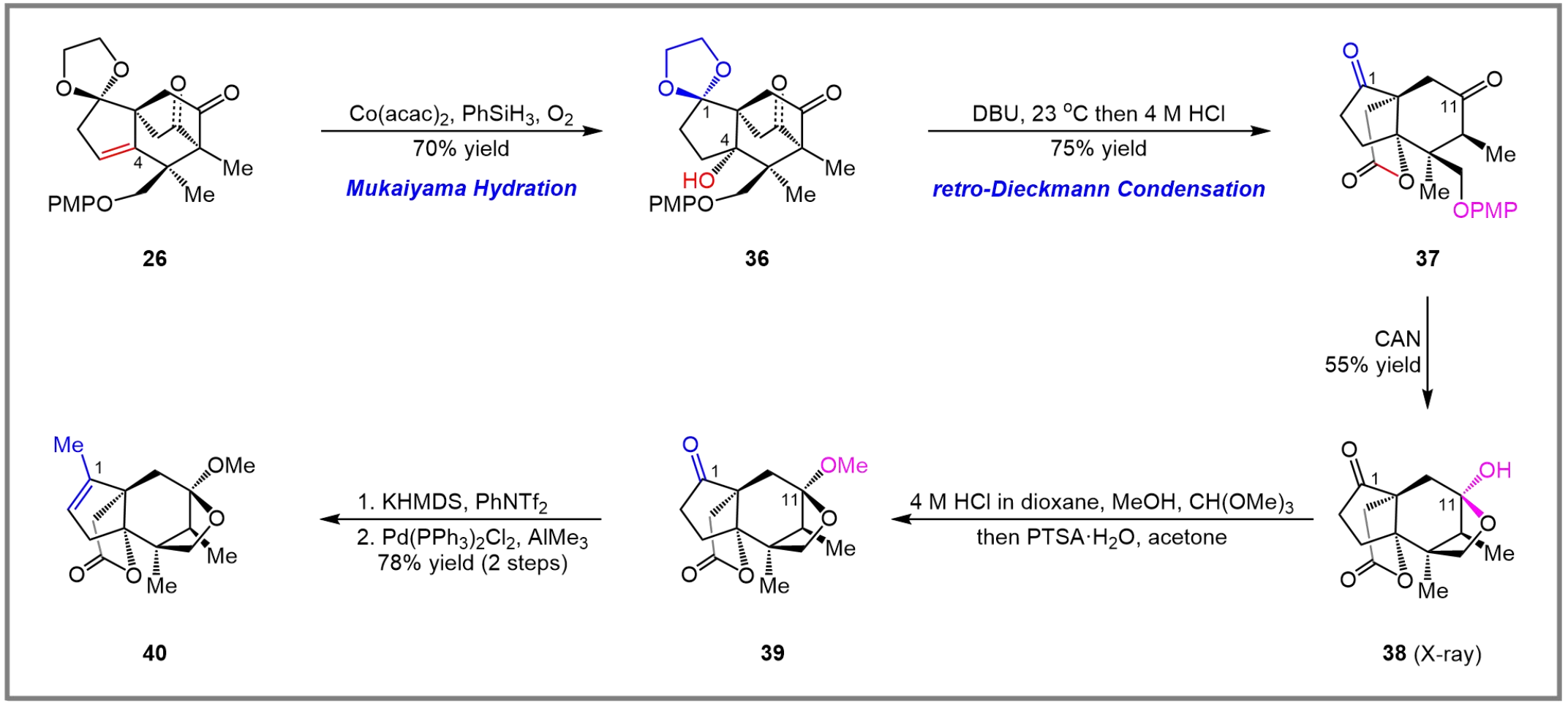

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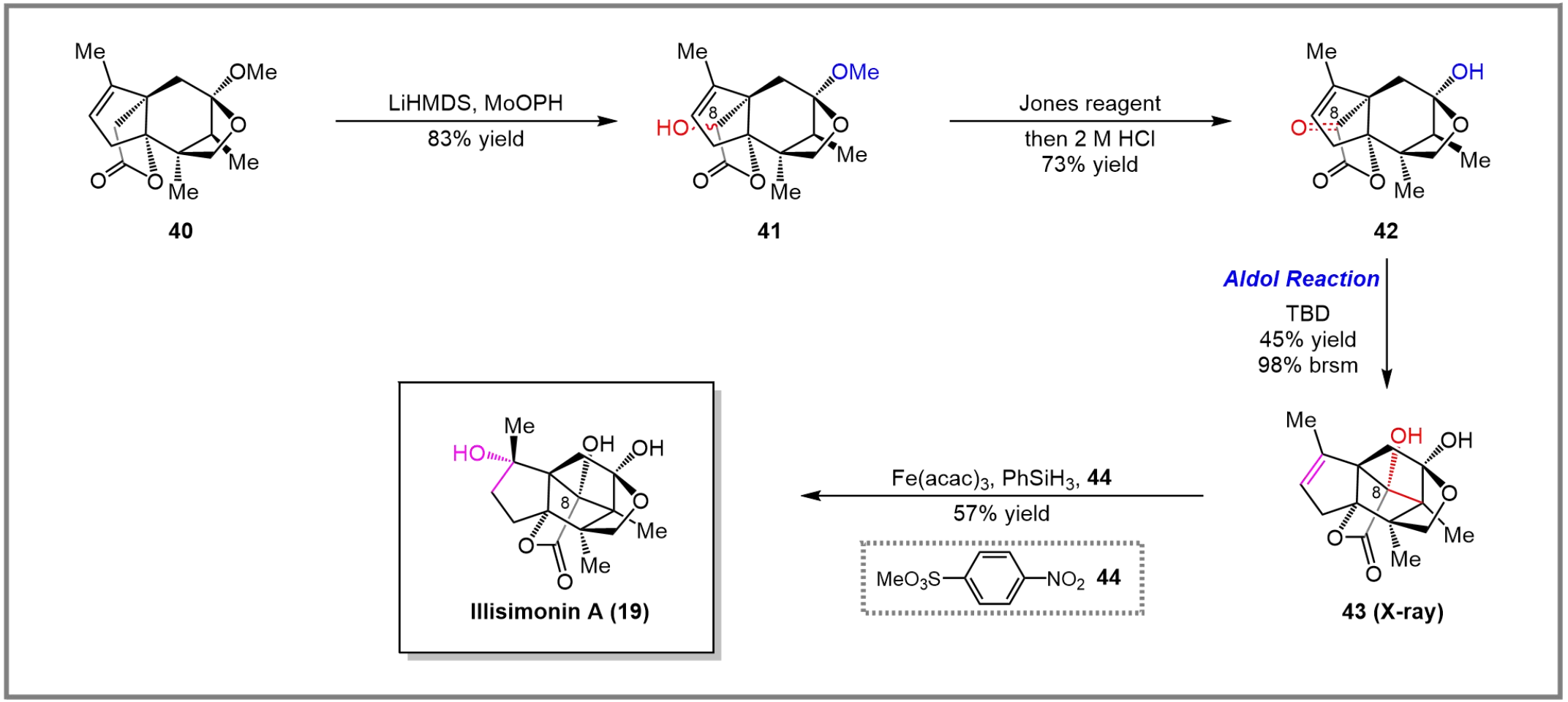

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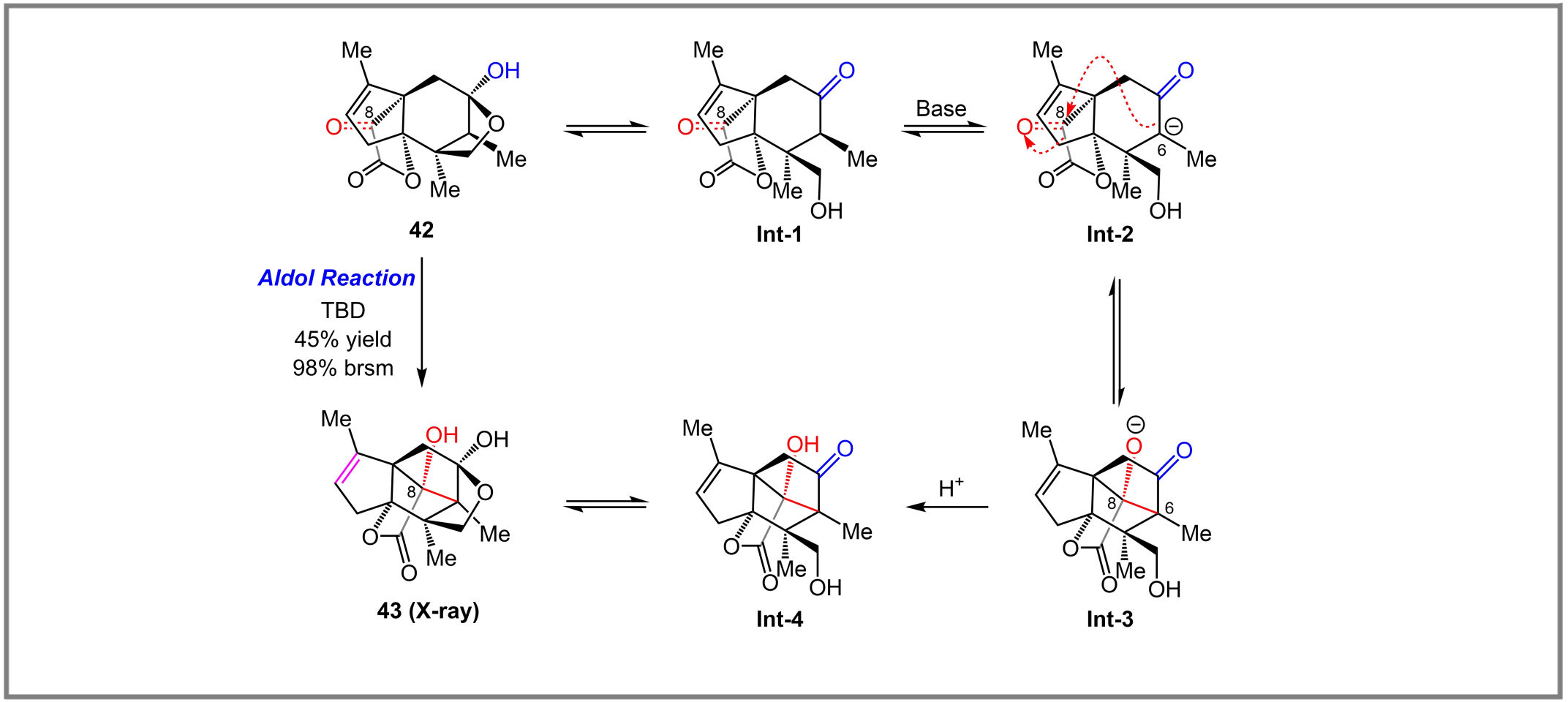
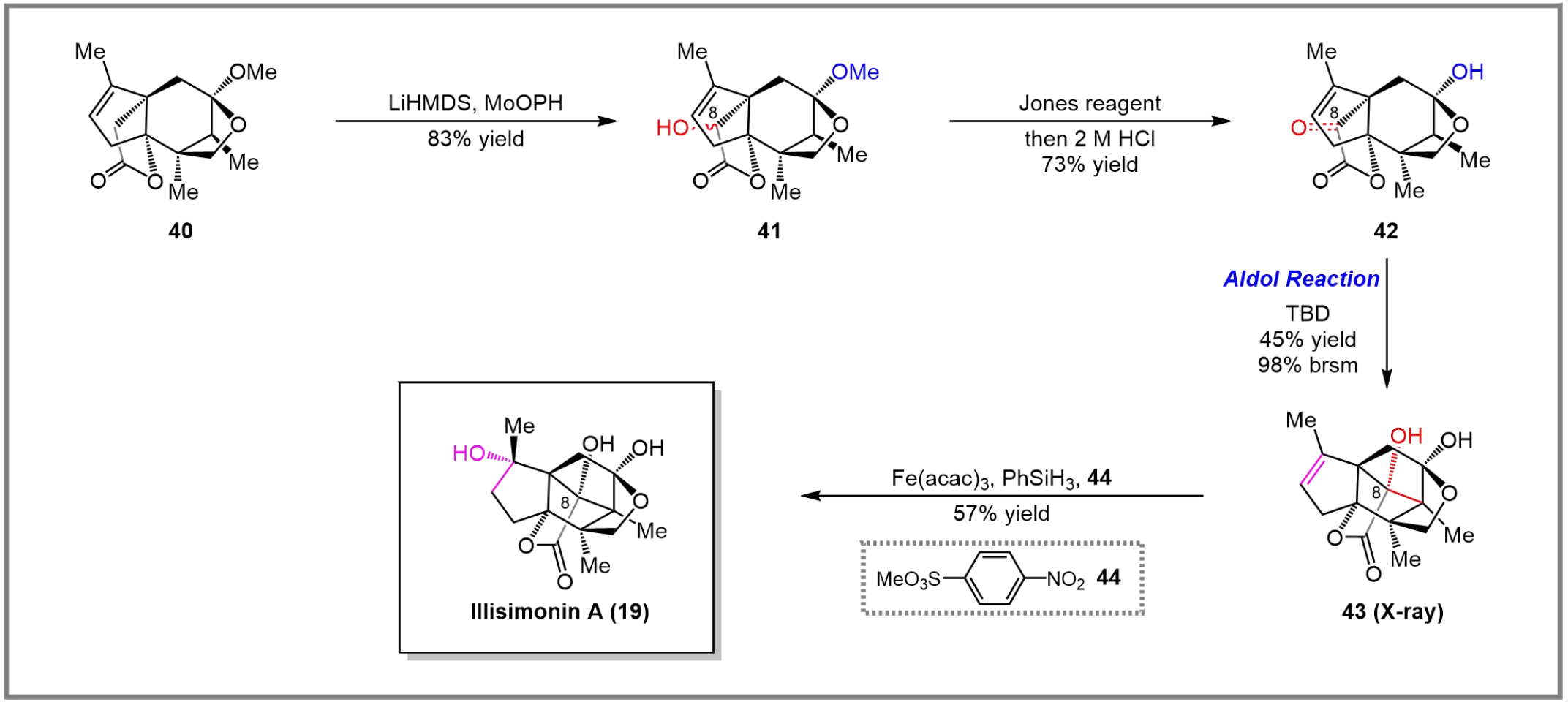
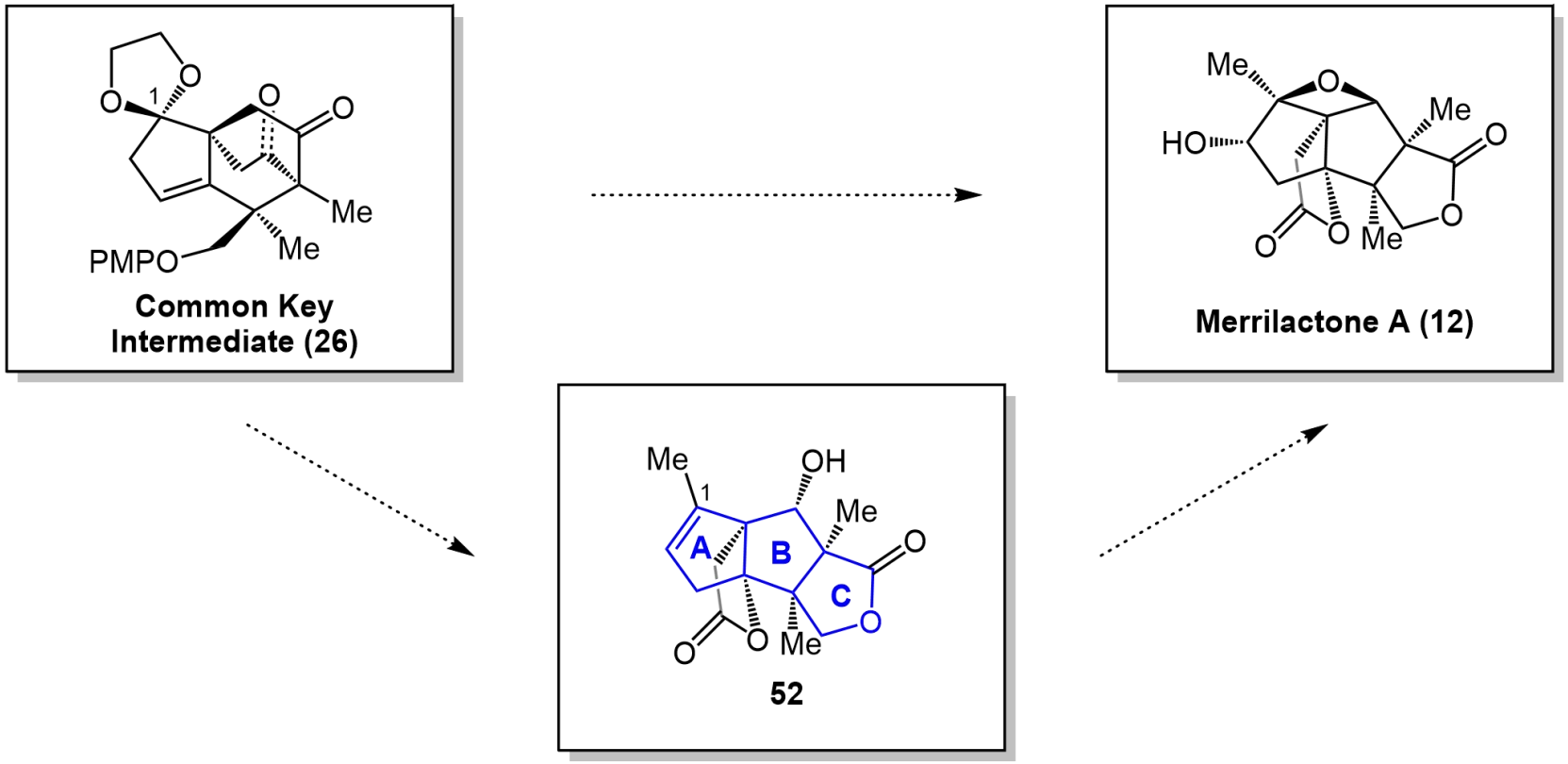


Synthesis of Illisimonin A

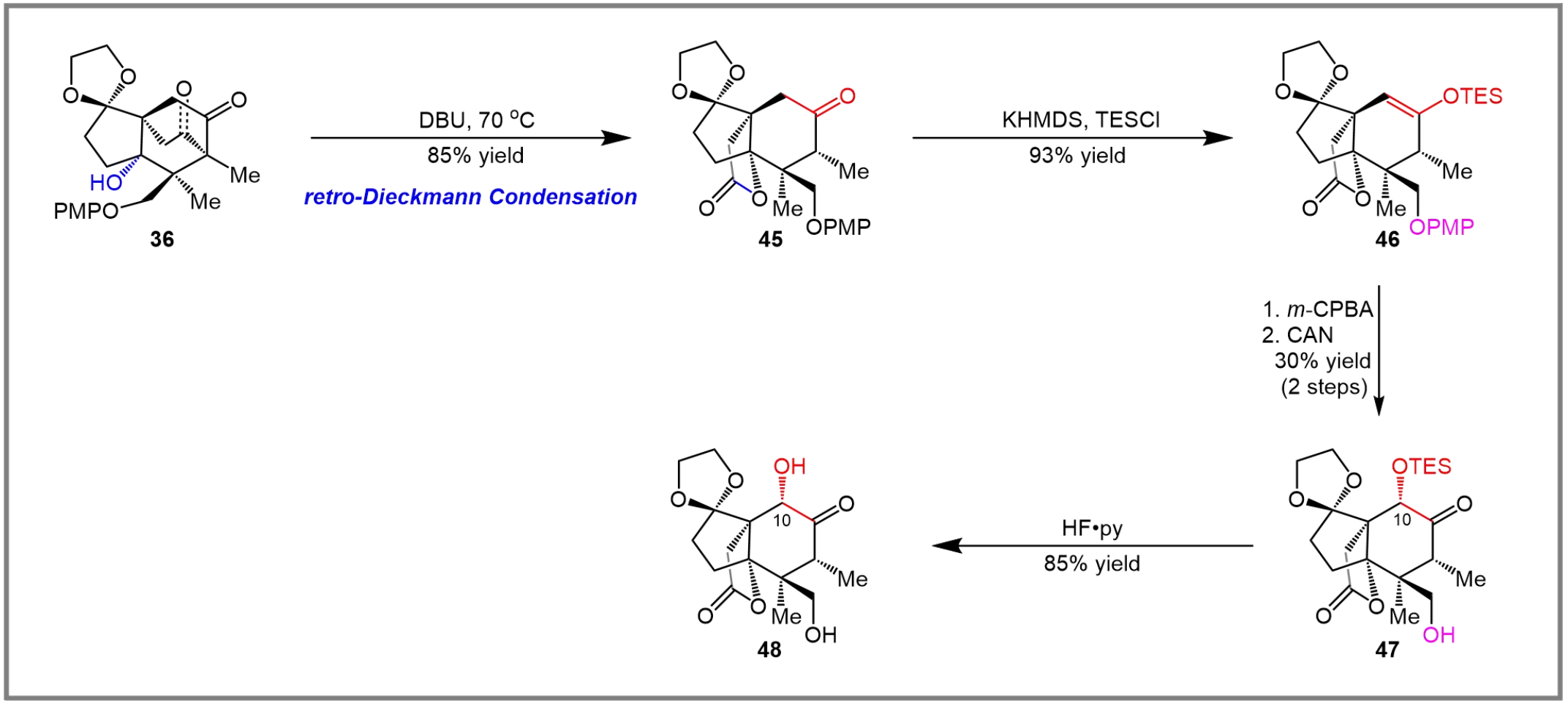


Synthesis of Merrilactone A



Chen, J.; Gao, P.; Yu, F.; Chen, Z.; Zhai, H.* *Angew. Chem. Int. Ed.* **2012**, *51*, 5897

Synthesis of the Carbon Scaffold of Merrilactone A



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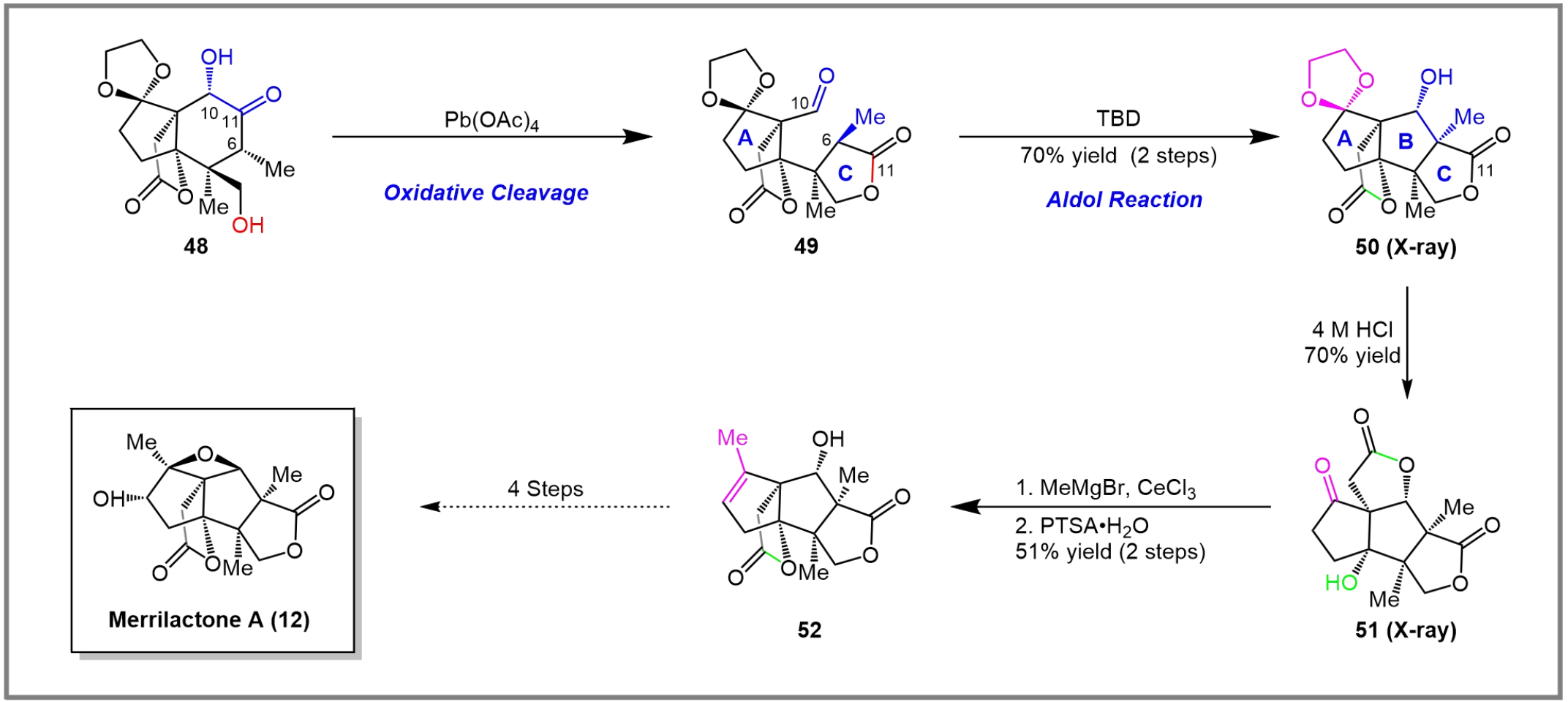
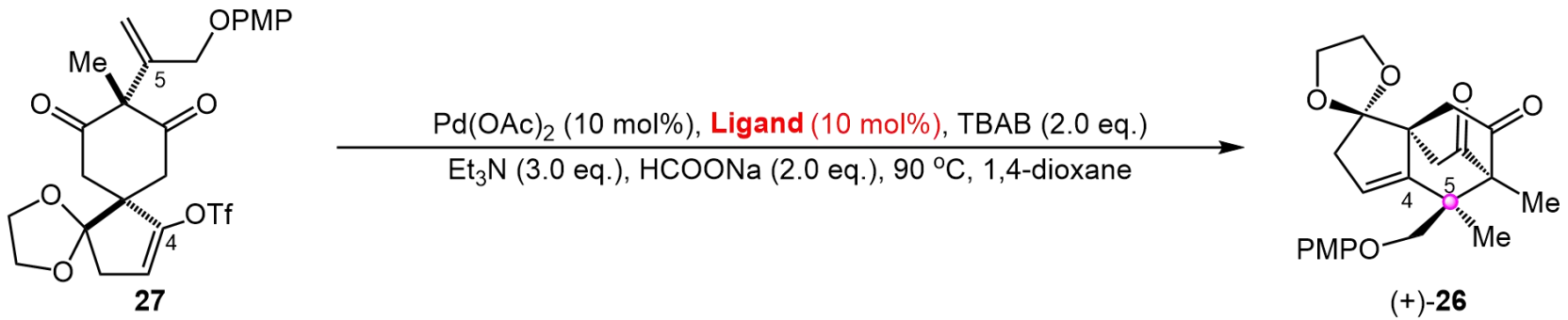


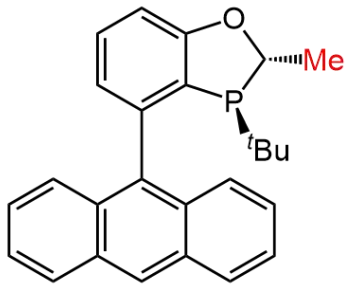
Optimization of the Asymmetric Reductive Heck Reaction

Screening the Ligands for the Asymmetric Reductive Heck Reaction

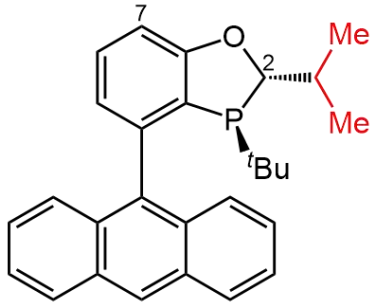


Optimization of the Asymmetric Reductive Heck Reaction

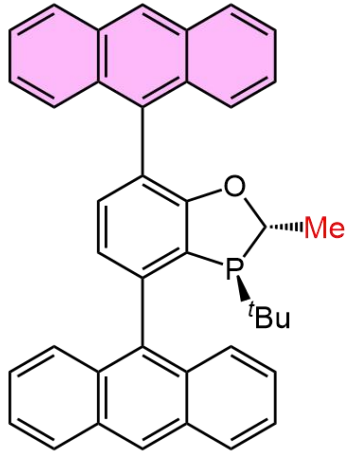
Optimization of Chiral Ligands for Asymmetric Reductive Heck Reaction



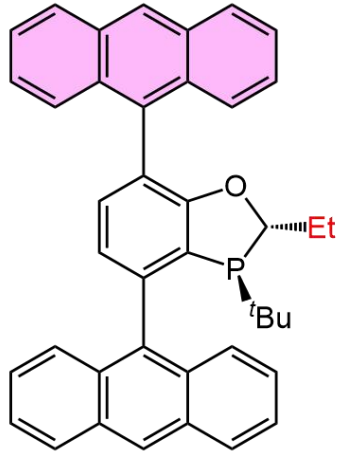
L1 : 37% yield, 7% ee



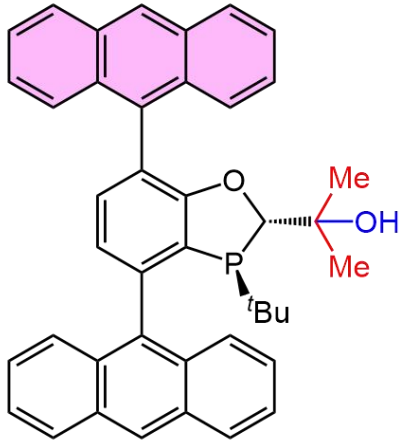
L2 : 39% yield, 5% ee



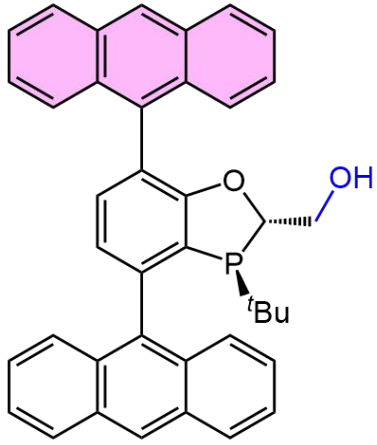
L3 : 33% yield, 11% ee



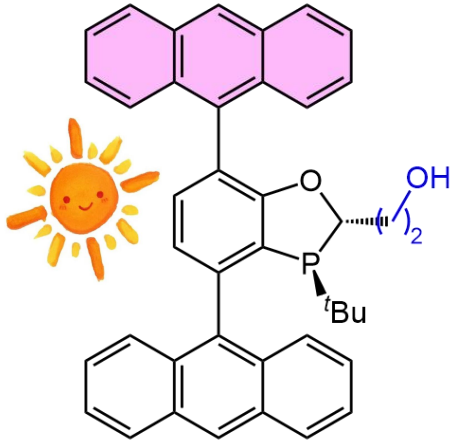
L4 : 32% yield, 20% ee



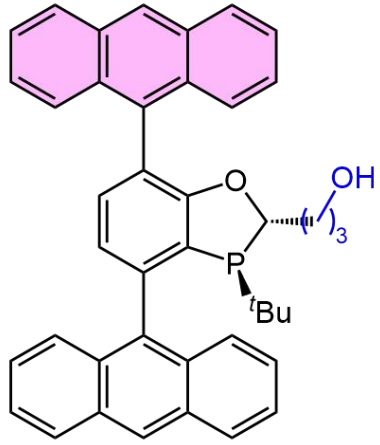
L5 : 30% yield, 50% ee



L6 : 31% yield, 43% ee



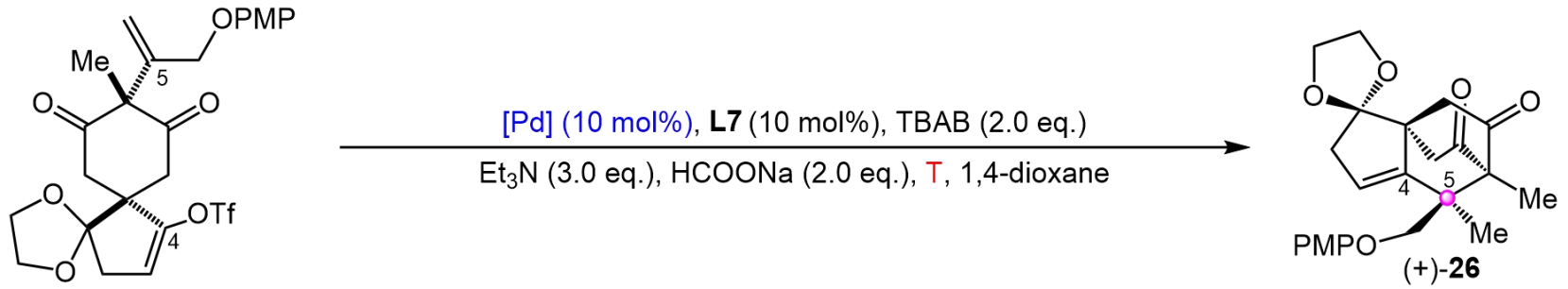
L7 : 23% yield, 60% ee



L8 : 27% yield, 40% ee

Optimization of the Asymmetric Reductive Heck Reaction

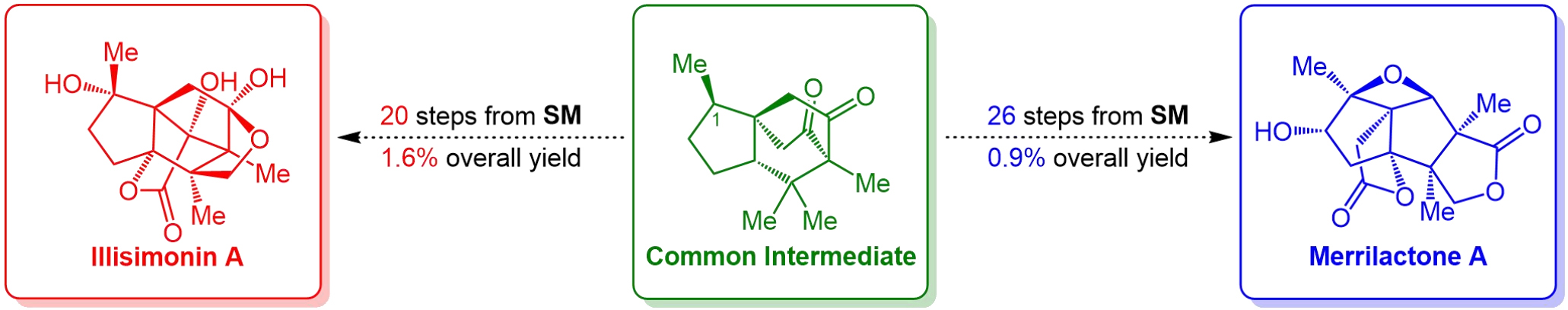
Optimization of Conditions for Asymmetric Reductive Heck Reaction of 27 Using L7 as Ligand



Entry	[Pd]	Ligand	T [°C]	Yield [%]	Ee [%]
1	$Pd(OAc)_2$	**L7**	90	23	60
2	$Pd_2(dba)_3$	**L7**	90	40	30
3	$Pd_2(dba)_3$	**L7**	80	23	82
4	$Pd_2(dba)_3$	**L7**	70	10	60

在最优条件下，以82%的ee值得到(+)-26，遗憾的是，仅有23%收率
难以满足后续的全合成需求，未能实现该家族天然产物的不对称合成

Summary



- ✓ **Illisimonin A and Merrilactone A were synthesized in 20 and 26 steps in the longest linear sequence, 1.6% and 0.9% overall yield respectively;**
- ✓ **The first example of syntheses of illicium sesquiterpenes with different carbon scaffolds from a common intermediate.**

Writing Strategy

☐ The First Paragraph

Illicium sesquiterpenes 的分离与分类

✓ **Illicium sesquiterpenes are a large number of structurally diverse natural products isolated from *Illicium* species plants. According to their modes of carbon scaffold connectivity, they could be categorized into.....**

Illicium sesquiterpenes 的生物活性

✓ **Some members of these natural products have been shown to possess potent neurite outgrowth promoting activity in primary cultured rat cortical neurons, which could be useful for the development of lead compounds for the treatment of neurodegenerative diseases.**

研究现状 以及引出本文工作

✓ **Owing to significant bioactivities and complex molecular architectures, they have attracted great attention from synthetic chemists. To date …… Herein, we report ……**

Writing Strategy

☐ The Last Paragraph

对合成方法
和思路进行总结

✓ In conclusion, we have proposed a plausible comprehensive biosynthetic pathway for illicium sesquiterpenes for the first time. The syntheses of illisimonin A and merrilactone A from key intermediate 26……Illisimonin A and merrilactone A were synthesized in 20 and 26 steps in the longest linear sequence, respectively.

开发了新手性膦配体

✓ A new type of P-chiral phosphorus ligand was also developed to enable key asymmetric intramolecular desymmetrizing reductive Heck reaction, and a maximum of 82% ee was obtained.

本文亮点：一个中间体
合成不同倍半萜

✓ This is also the first example of syntheses of illicium sesquiterpenes with different carbon scaffolds from a common intermediate.

Representative Examples

- ✓ We reason that the *allo*-cedryl cation could be oxidized to dicarbonyl compound 7 first, which is the key intermediate in the biosynthetic pathway of illicium sesquiterpenes. (n. 原因，理由 v.推理，推论出)

- ✓ There might be a hydrogen bond between the nitroaromatic compound 44 and C8 hydroxy group in 43, which led to the inversion of selectivity at XX position and gave high diastereoselectivity in the Mukaiyama hydration. (导致XX位置的选择性反转且具有优异的非对映选择性)

Acknowledgment

Thanks for your attention!