Literature Report 5

Collective Asymmetric Total Synthesis of Cephalotaxus Alkaloids

Reporter: Wen-Jun Huang

Checker: Li-Xia Liu

Date: 2021-11-01

Kim, S. *et al. Angew. Chem. Int. Ed*. **2021**, *60*, 12060
Stoltz, B. M. *et al. J. Org. Chem.* **2007**, *72*, 7352

CV of Prof. Sanghee Kim

Background:

- **1984-1988** B.S., Seoul National University (SNU)
- **1988-1990** M.S., SNU
- **1992-1997** Ph.D., University of Pennsylvania
- **1997-1998** Postdoc., The Scripps Research Institute
- **1998-1999** Senior Research Scientist
- **1999-2008** Assistant & Associate Professor, SNU
- **2008-Now** Professor, SNU

Research:

- Total synthesis of natural products
- Medicinal chemistry and drug discovery
- Electrochemical & photochemical bioorganic chemistry

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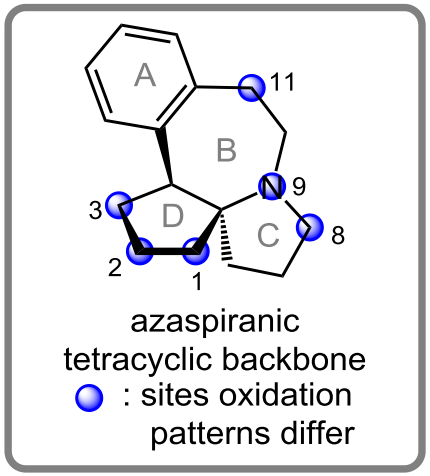
2 Total Synthesis of Cephalotaxus Alkaloids

3 Total Synthesis of Cephalotaxine (1)

4 Summary

Introduction

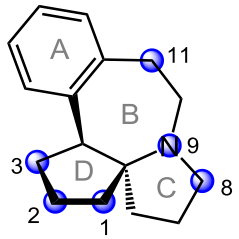


Cephalotaxus alkaloids

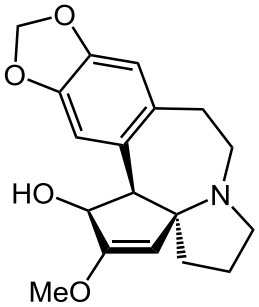
Cephalotaxus

- Cephalotaxus alkaloids exhibit antileukemic and antitumor activities.
- Cephalotaxus alkaloids contain an azaspiranic tetracyclic scaffold.
- More than 70 compounds have been isolated from natural sources so far.

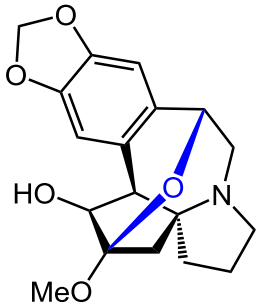
Introduction



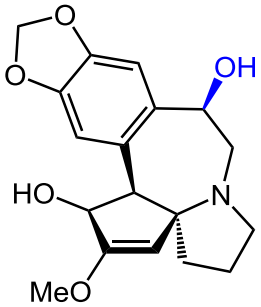
azaspiranic tetracyclic backbone
: sites oxidation patterns differ



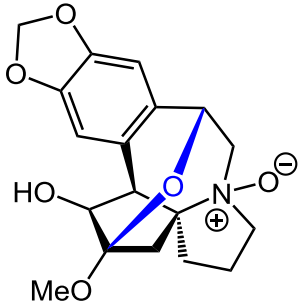
cephalotaxine (**1**)



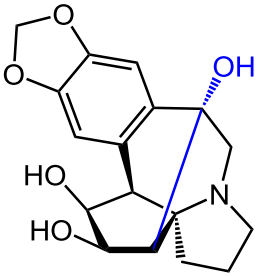
drupacine (**3**)



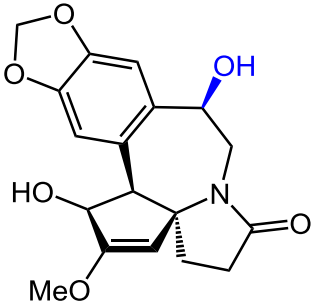
11-hydroxycephalotaxine (**4**)



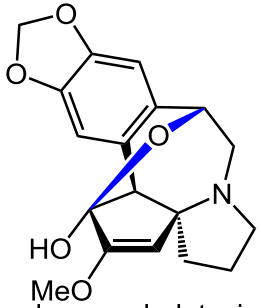
cephalancetine B (**8**)



cephalocyclidin A (**10**)

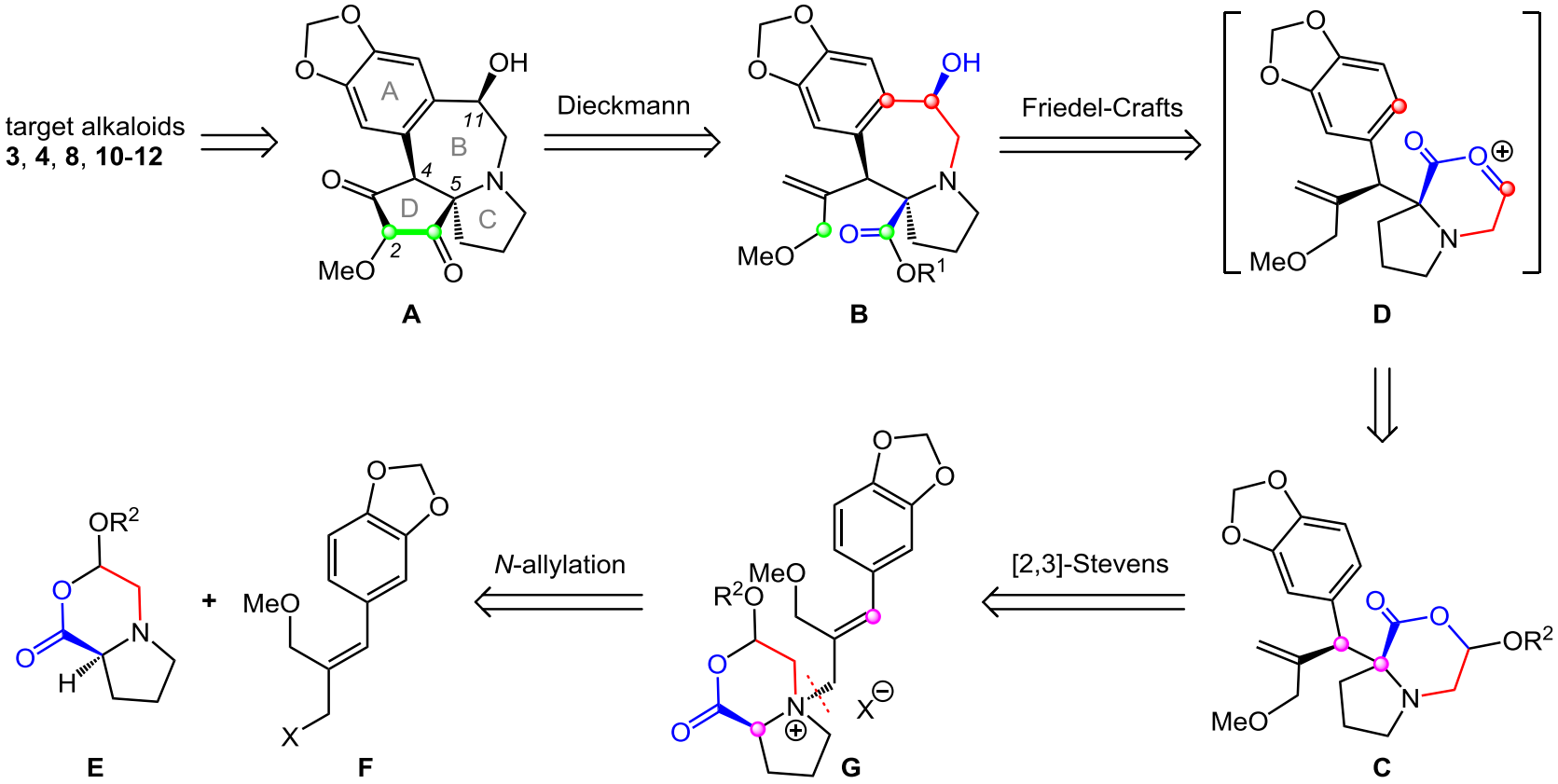


torreyafargesine A (**11**)



11-hydroxycephalotaxinone hemiketal (**12**)

Retrosynthetic Analysis



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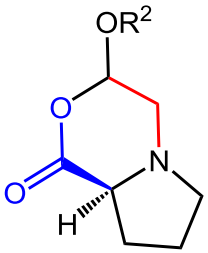
Synthesis of 17 and 16



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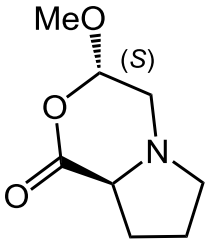

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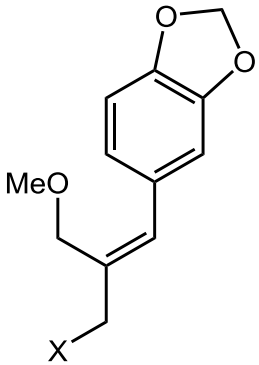

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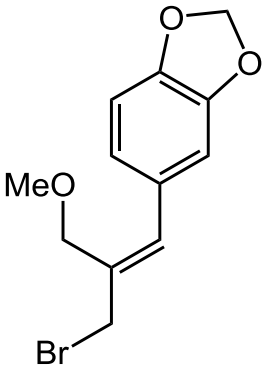
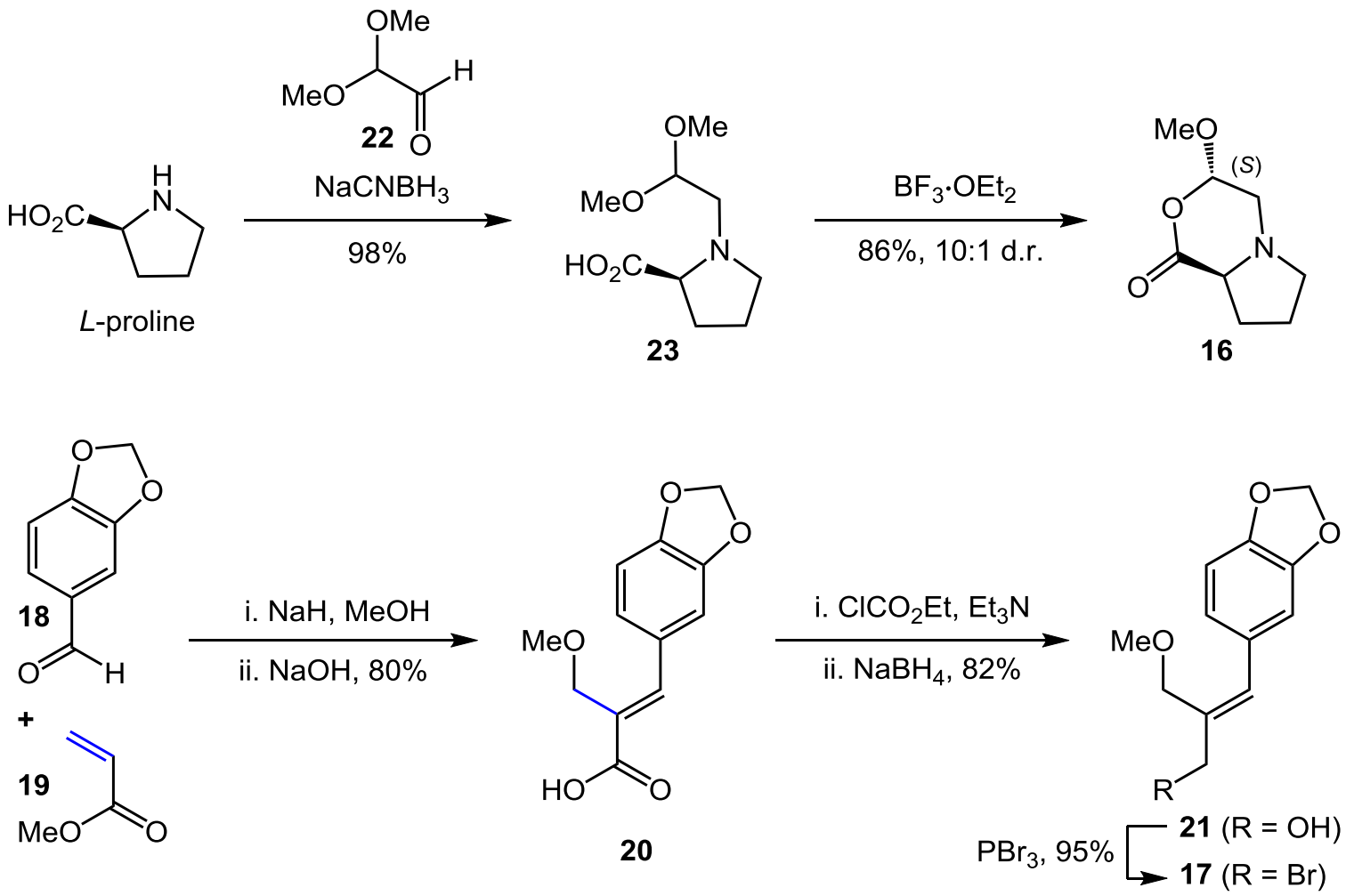
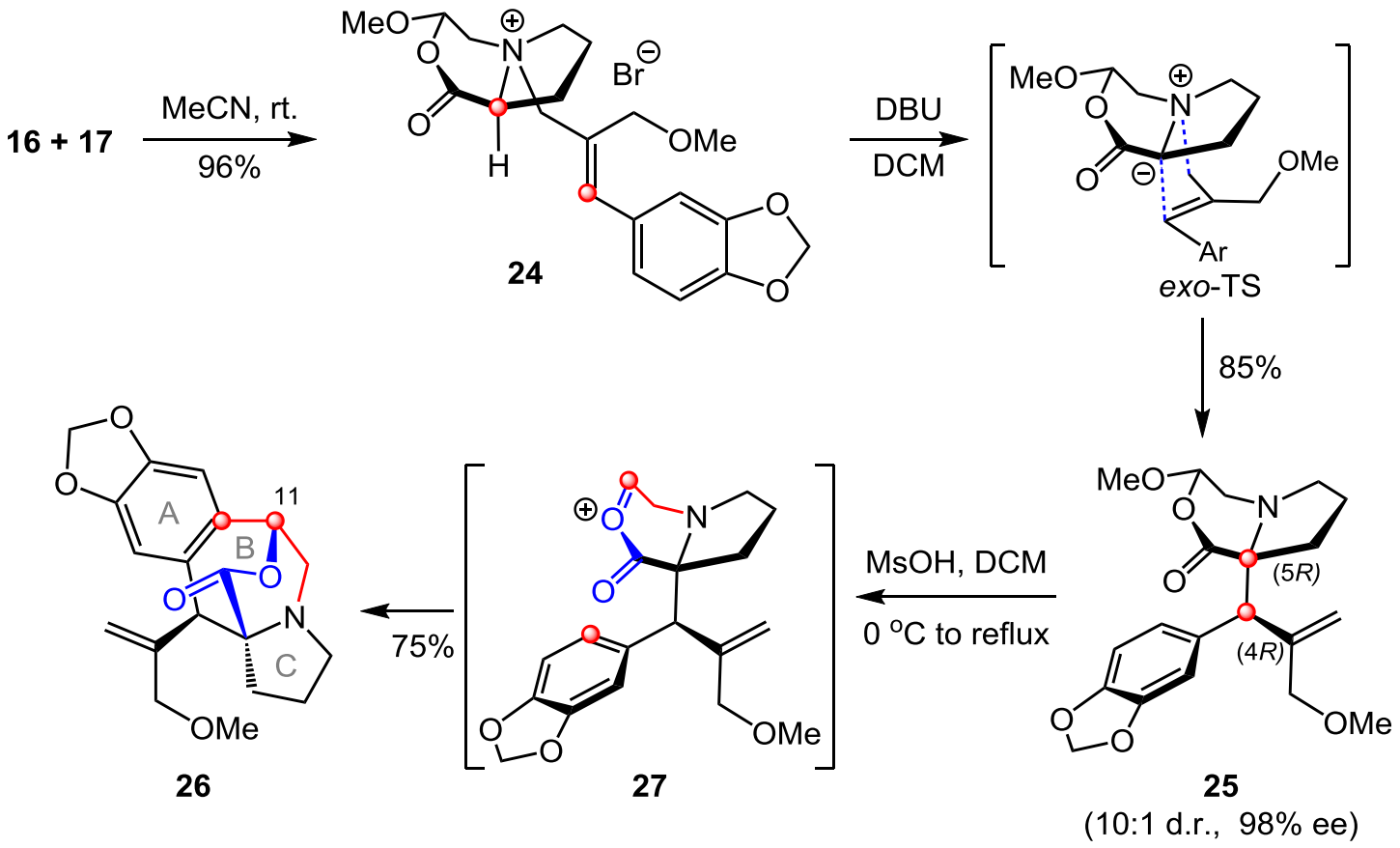


17

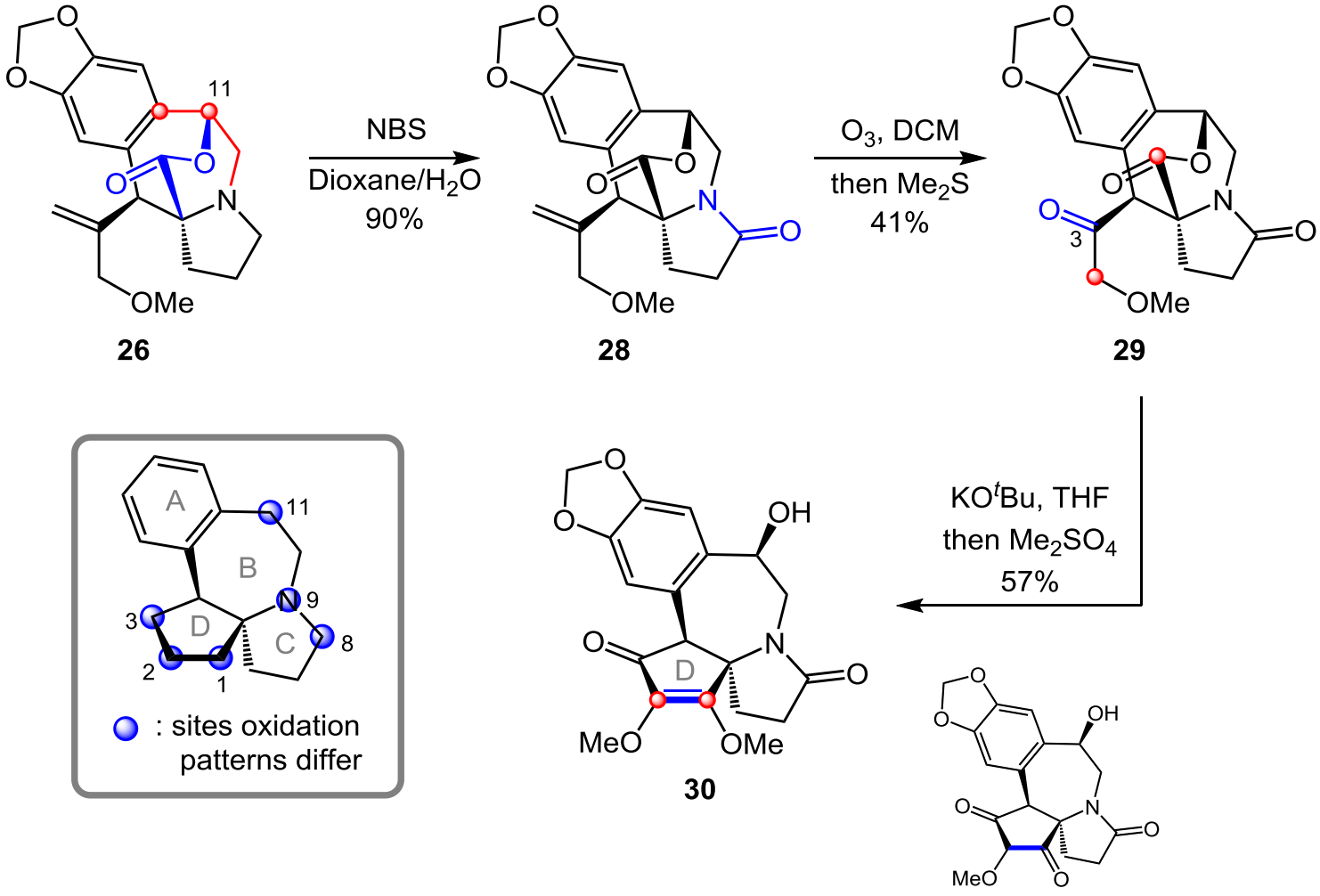
Synthesis of 17 and 16



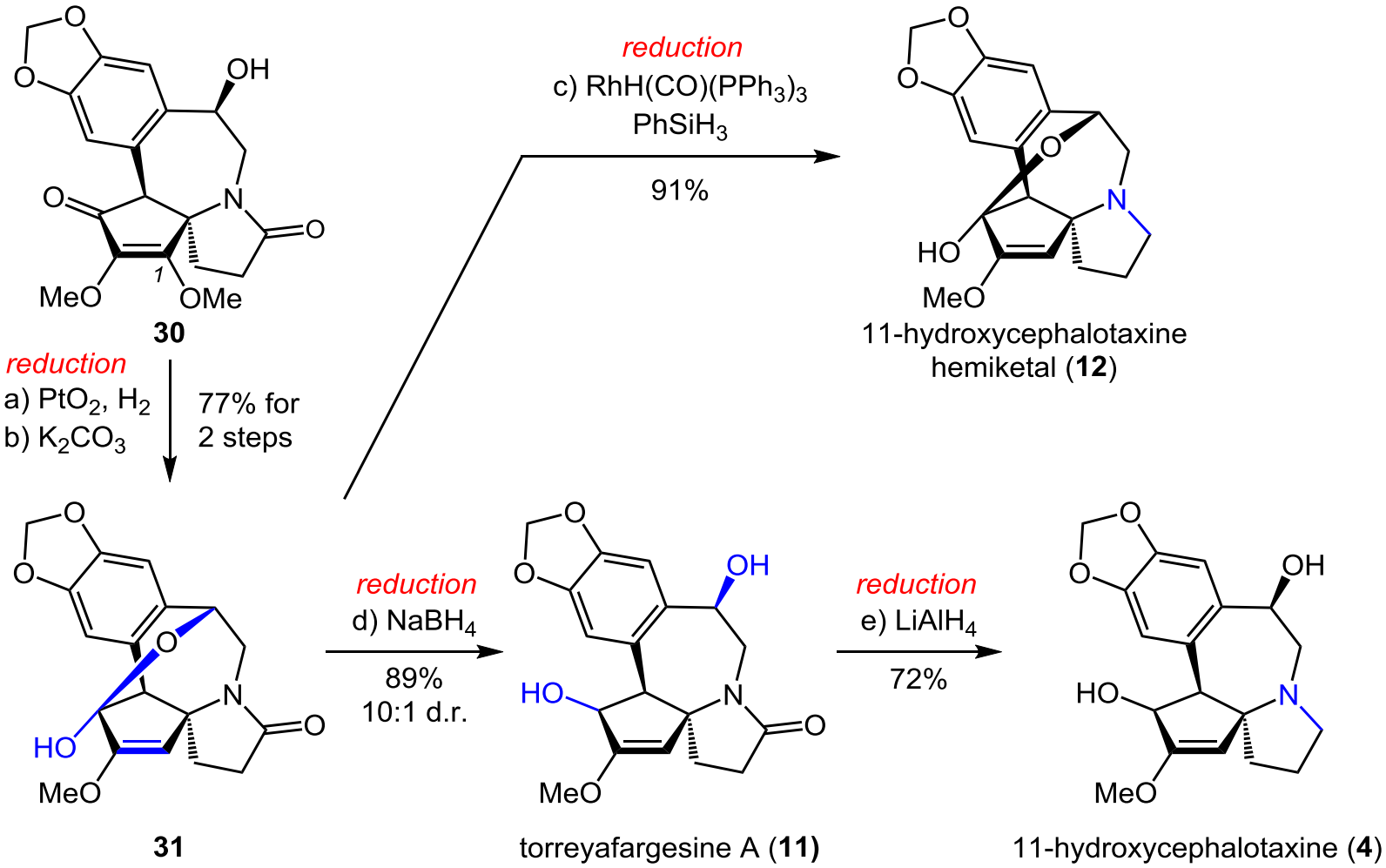
Synthesis of 26



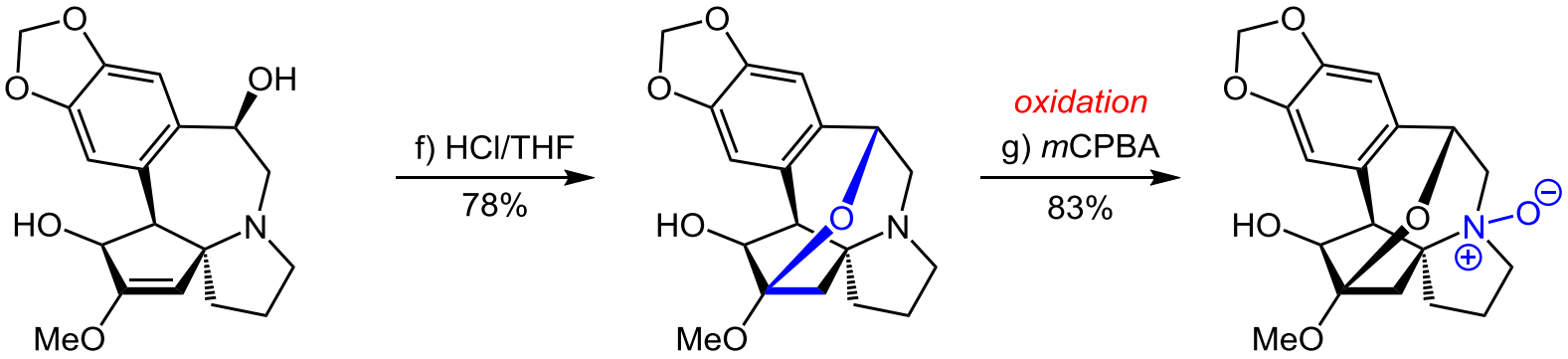
Synthesis of Advanced Intermediate 30



Divergent Synthesis of Cephalotaxus Alkaloids

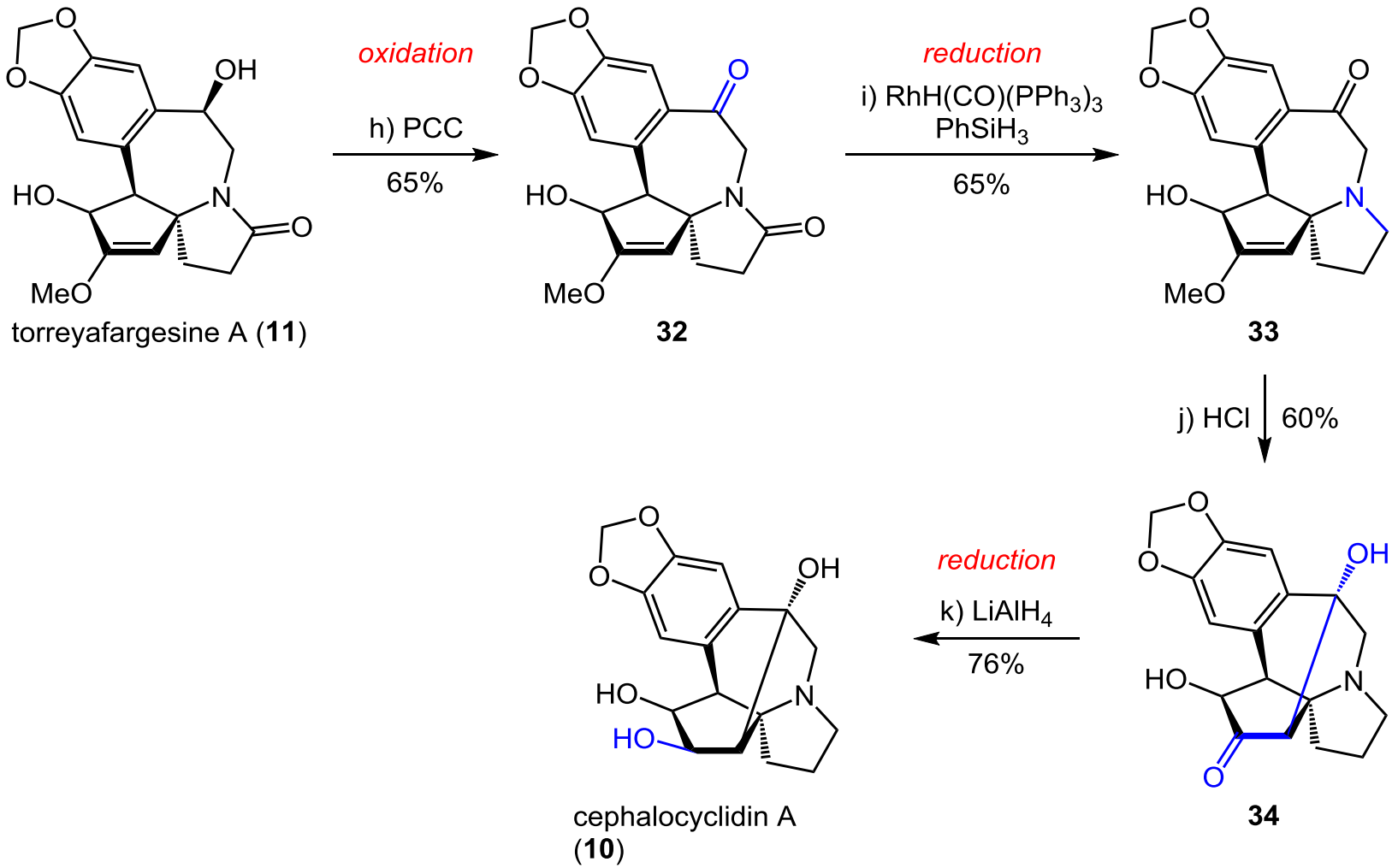


Divergent Synthesis of Cephalotaxus Alkaloids

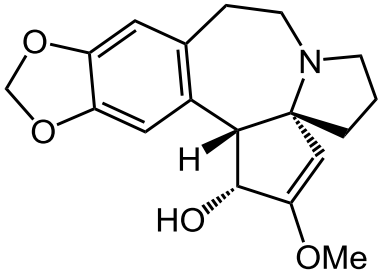


11-hydroxycephalotaxine (**4**) drupacine (**3**) cephalancetine B (**8**)

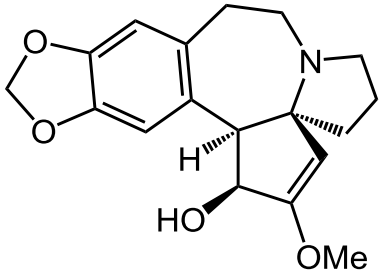
Divergent Synthesis of Cephalotaxus Alkaloids



Synthesis of (+)- and (-)-Cephalotaxine 1



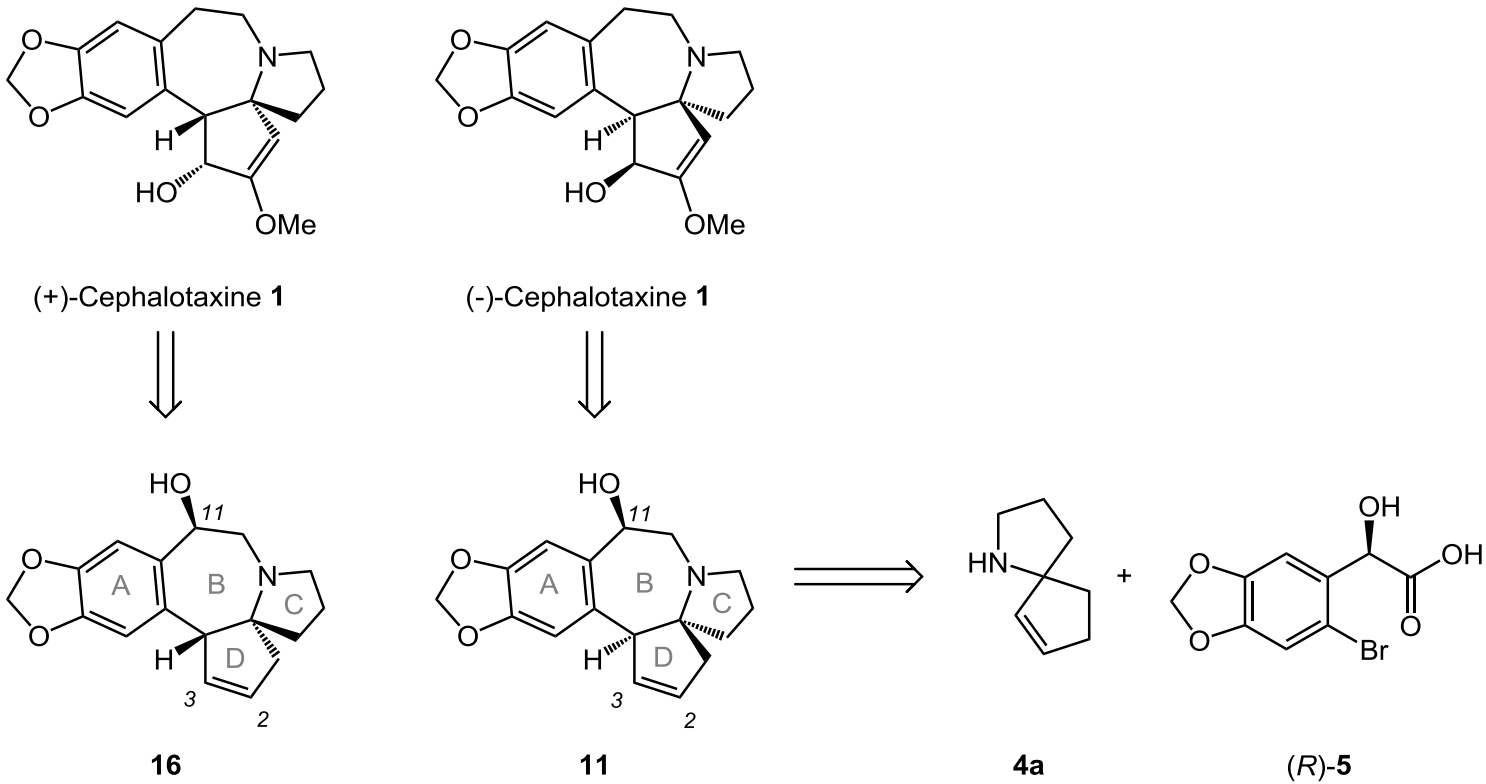
(+)-Cephalotaxine **1**



(-)-Cephalotaxine **1**

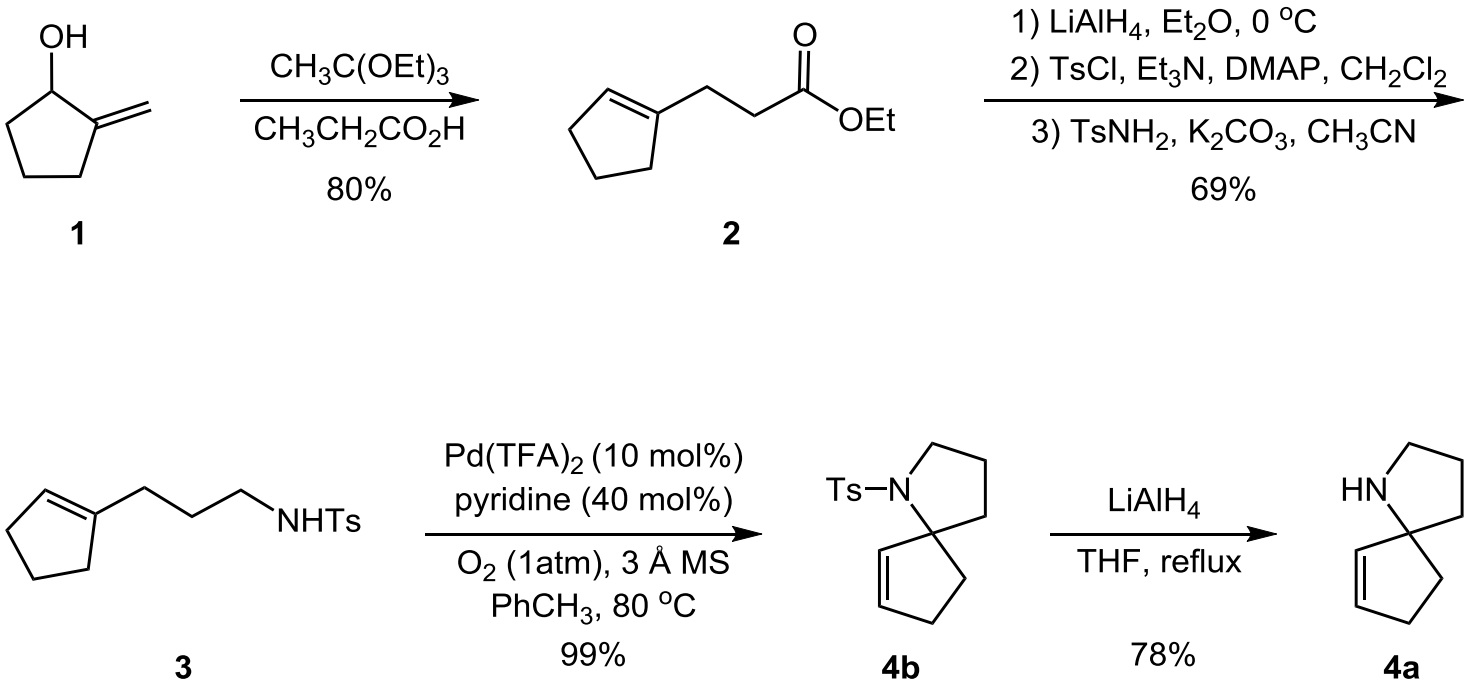
Stoltz, B. M. *et al. J. Org. Chem.* **2007**, *72*, 7352

Retrosynthetic Analysis

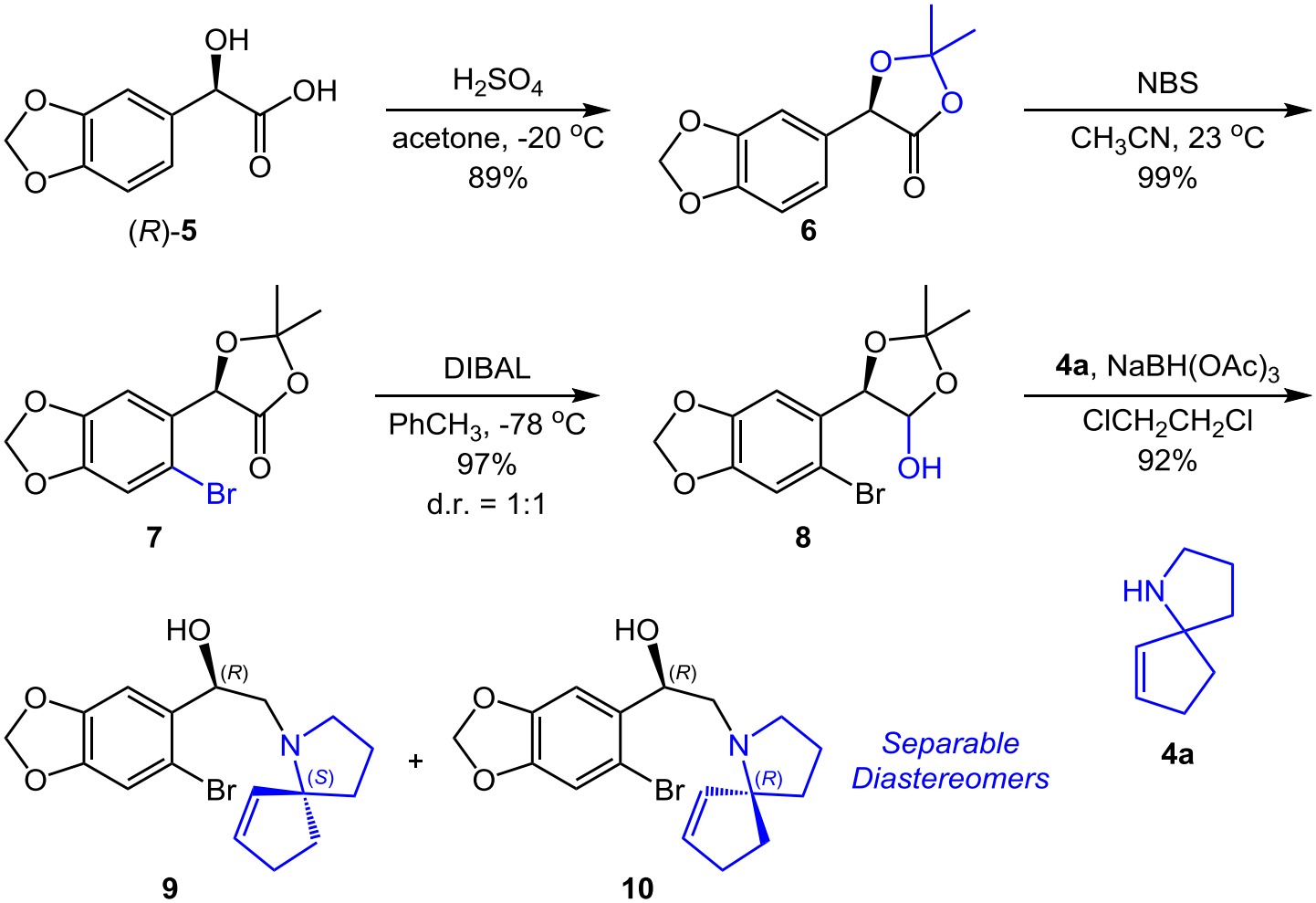


Stoltz, B. M. *et al. J. Org. Chem.* **2007**, *72*, 7352
Mori, M. *et al. J. Org. Chem.* ***1995***, *60*, 115

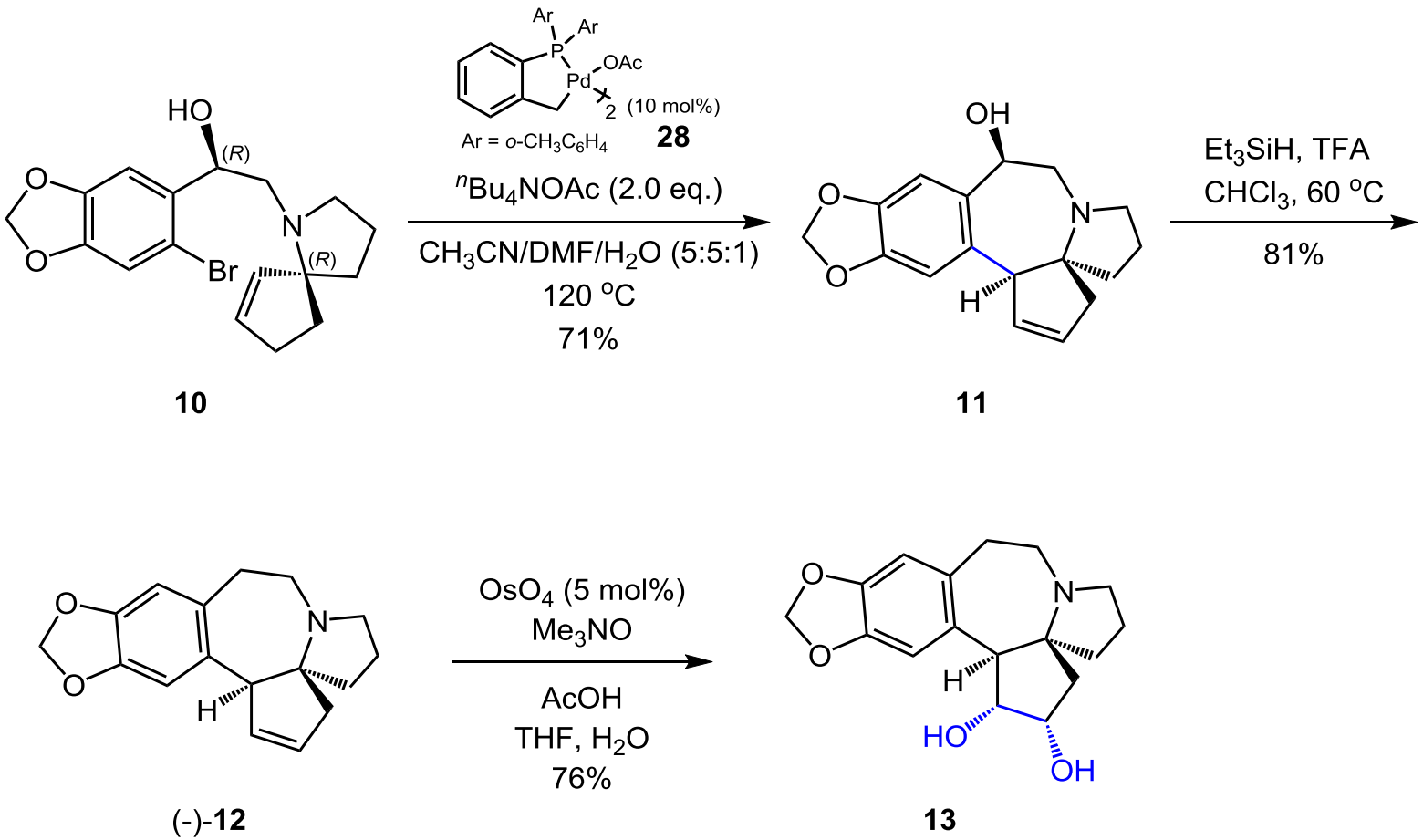
Synthesis of Spirocyclic Amine 4a



Synthesis of 9 and 10

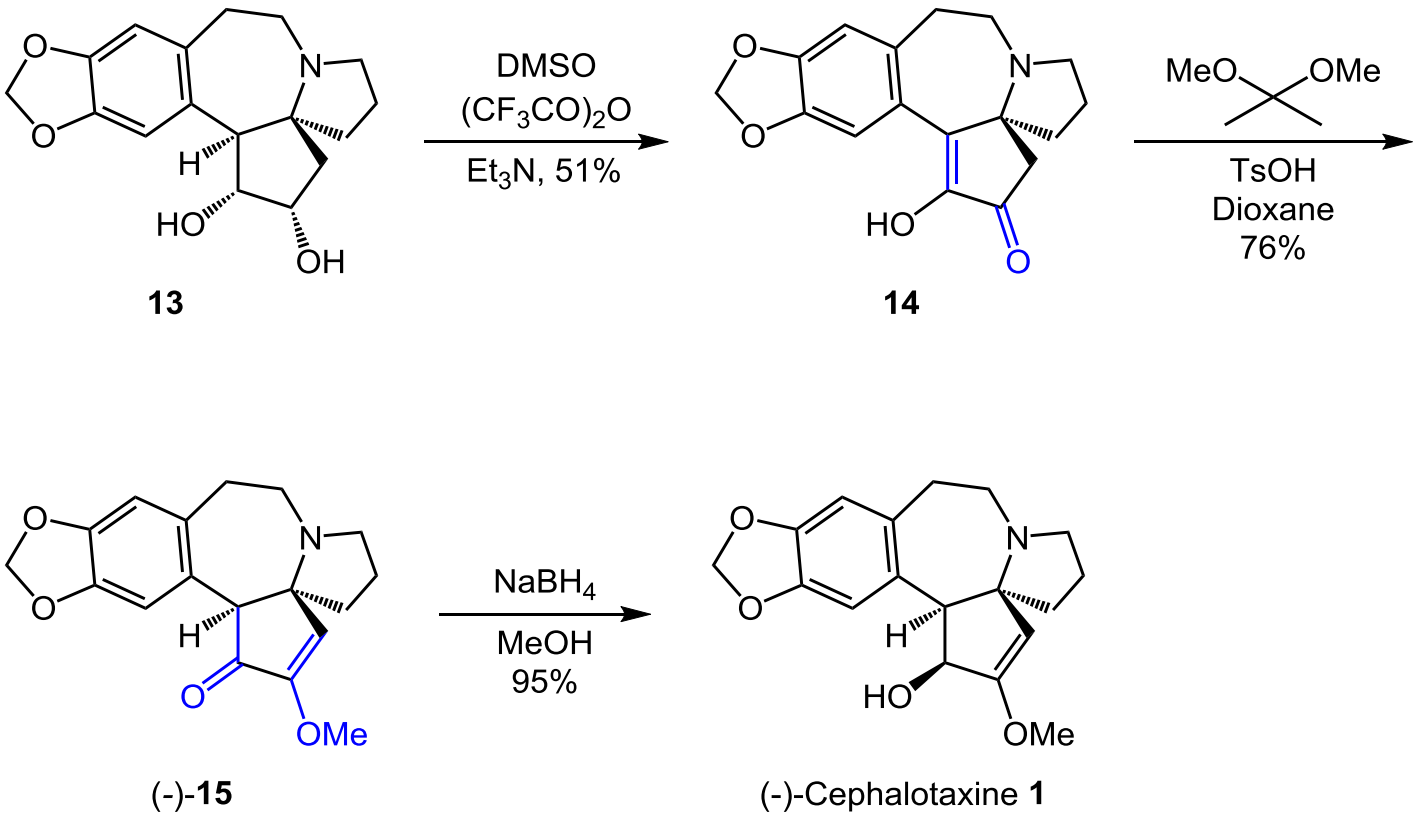


Synthesis of 13



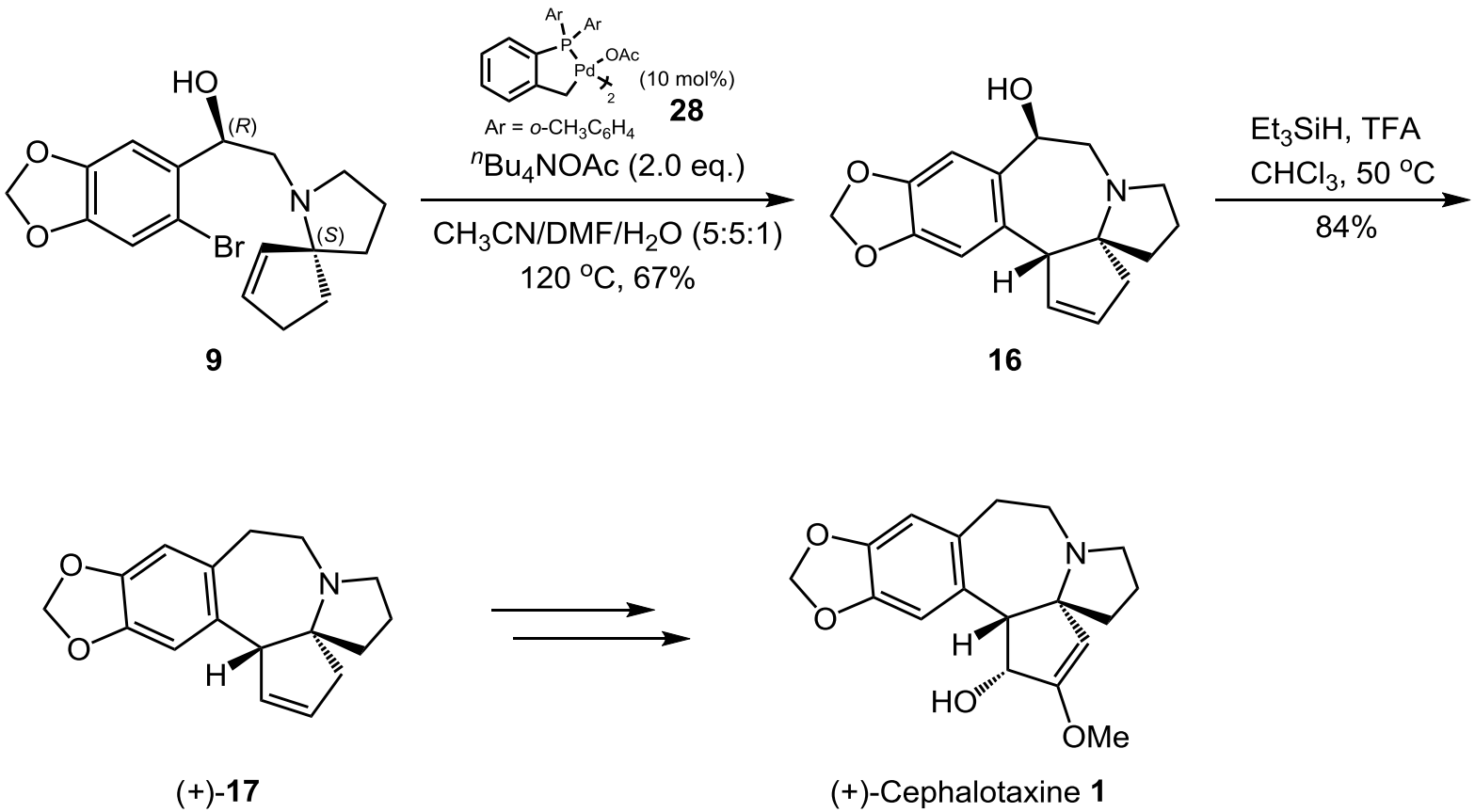
Mori, M. *et al. J. Org. Chem.* ***1995***, *60*, 115

Synthesis of (-)-Cephalotaxine

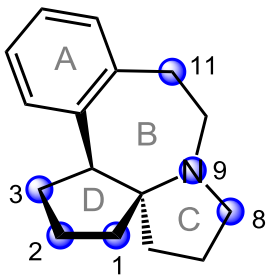


Mori, M. *et al. J. Org. Chem.* ***1995***, *60*, 115

Synthesis of (+)-Cephalotaxine



Summary



azaspiranic
tetracyclic backbone
: sites oxidation
patterns differ

C-11 Oxygenated Cephalotaxus Alkaloids

- 11-15 steps from *L*-proline;
- Asymmetric total synthesis of six C-11 oxygenated Cephalotaxus alkaloids;
- Diastereoselective *N*-alkylation, stereospecific Stevens rearrangement and intramolecular Friedel–Crafts reaction.

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(-) and (+)-Cephalotaxine 1

- 6 steps from (*R*)-**5**;
- Stereodivergent formal total synthesis of (+)- and (-)-Cephalotaxine **1**;
- Reductive amination, and an intramolecular Heck reaction.

Stoltz, B. M. *et al. J. Org. Chem.* **2007**, *72*, 7352

The First Paragraph

写作思路

Cephalotaxus生物碱的
生物活性和结构特征

↓

Cephalotaxus生物碱的
代表性成员以及结构差异

The First Paragraph

For half a century, Cephalotaxus alkaloids have been popular synthetic targets due to their intriguing structures and biological activities. The alkaloids of this family have several interesting biological activities, including antileukemic and antitumor activities. The characteristic structural feature of these alkaloids is an azaspiranic tetracyclic scaffold. More than 70 compounds have been isolated from natural sources so far. The first isolated and most representative member of this family is (-)-cephalotaxine (**1**). One of its naturally occurring ester derivatives, homoharringtonine (**2**), was approved by the FDA in 2012 as an antileukemia drug.

The First Paragraph

The other representative member is drupacine (**3**) which was isolated from Cephalotaxus harringtonia. Unlike cephalotaxine (**1**), this alkaloid possesses an oxygen function at C-11. 11-Hydroxycephalotaxine (**4**), which is readily converted to **3** under acidic conditions, was also isolated from the same plant from which **3** was isolated. To date, ten C-11 oxygenated Cephalotaxus alkaloids have been isolated, including three ester derivatives of **3** and an *N*-oxide derivative cephalancetine B (**8**). A dimeric alkaloid cephalancetine D (**9**) and pentacyclic cephalocyclidin A (**10**) also belong to this subset.

The First Paragraph

Recently, torreyafargesine A (**11**) and 11-hydroxycephalotaxinone hemiketal (**12**) were identified from Torreya fargesii Franch as new members of the C-11 oxygenated subset. The major structural differences among these alkaloids are the oxidation patterns on their backbone. The biological activities of this subset of alkaloids have not yet been thoroughly explored presumably because of the limited supply from nature.

The Last Paragraph

写作思路

工作总结

↓

全合成中的关键步骤

↓

工作的意义

The Last Paragraph

In conclusion, we have achieved stereoselective asymmetric total synthesis of six C-11 oxygenated Cephalotaxus alkaloids in 11–15 steps from *L*-proline (12–16 steps from piperonal). The total number of steps from commercially available materials are comparable to those reported for asymmetric synthesis of Cephalotaxus alkaloids without an oxygen at C-11. Our synthesis minimized the need for protecting-group manipulations. *L*-Proline was utilized both as a starting material and as the only chirality source to generate all the requisite stereocenters. Key to the success of this concise synthesis was a three-step sequential transformation of the proline derived nitrogen-fused bicycle **16** into the far more complex ring structure **26** with chirality propagation.

The Last Paragraph

This complexity-generating sequence involved an *N*-allylation, [2,3]-Stevens rearrangement, and intramolecular Friedel–Crafts reaction via an unusual AOI intermediate. The azaspiranic tetracyclic scaffold of Cephalotaxus alkaloids was readily constructed from **26**. Using **30** as an advanced intermediate, the total synthesis of six target alkaloids was completed without problem of skeletal cleavage by a series of selective oxidation state adjustments. This synthesis presents a good example of divergent total syntheses of complex natural products and an attractive strategy in terms of chiral economy.

The Last Paragraph

The concise synthetic route to C-11 Cephalotaxus alkaloids would enable investigations into their biological activities, which have been relatively less explored. Further applications of the proline-derived nitrogen-fused bicycle **16** and its related acyclic amino acid derivatives to the synthesis of complex molecules are underway in our group.

Representative Examples

We expected that AOI intermediate **27** would be formed from **25** under acidic conditions, analogous to the widely applied method for the formation of the *N*-acyliminium ion from *N*-acyl hemiaminal ether. (类似于……)

Prior to the oxidative cleavage of the methylene moiety of **26** to afford the biscarbonyl substrate for the Dieckmann ring closure. (在……之前)

According to NMR analysis, the obtained product **31** predominantly existed in a hemiketal form.（主要地，显著地）

As mentioned above (如上所述)

Acknowledgement

Thanks
for your attention