The Daphniphyllum Alkaloids: Total Synthesis of (–)-Calyciphylline N

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1.Introduction

1-1. (–)-Calyciphylline N

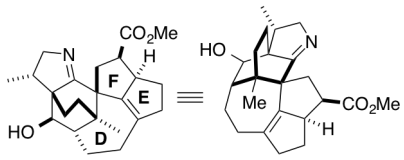


Figure1. Structure of (–)-Calyciphylline N (**1**)

• (–)-Calyciphylline N (**1**), a member of the daphniphyllum alkaloids, was isolated from leaves and stems of *Daphniphyllum calycinum* by Kobayashi in 2008.[1]

• Daphniphyllum alkaloids display diverse biological activities, including anticancer, antioxidant and vasorelaxation(血管弛緩作用).[2]

• **1** has a highly complex polycyclic skeleton with six contiguous stereocenters.

1-2. Background

• Development of a strategy to construction of DEF ring that appears in approximately half of the *daphniphyllum* family of more than 200 members[3]

• Few calyciphyllines families have been synthesized, and **1** remained as a target.

1-3. Strategy

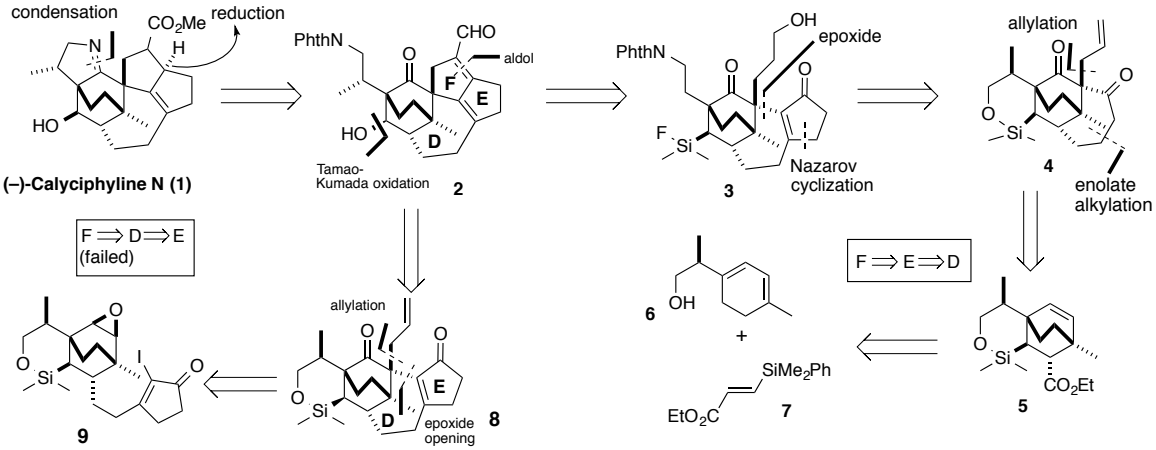


Figure2. Retrosynthetic analysis.

•Highlights of the synthesis include Diels-Alder reaction, allylation, Nazarov cyclization and diastereoselective hydrogenation.

2.Results and Discussion

2-1. Formation of bicyclo[2.2.2]octane core

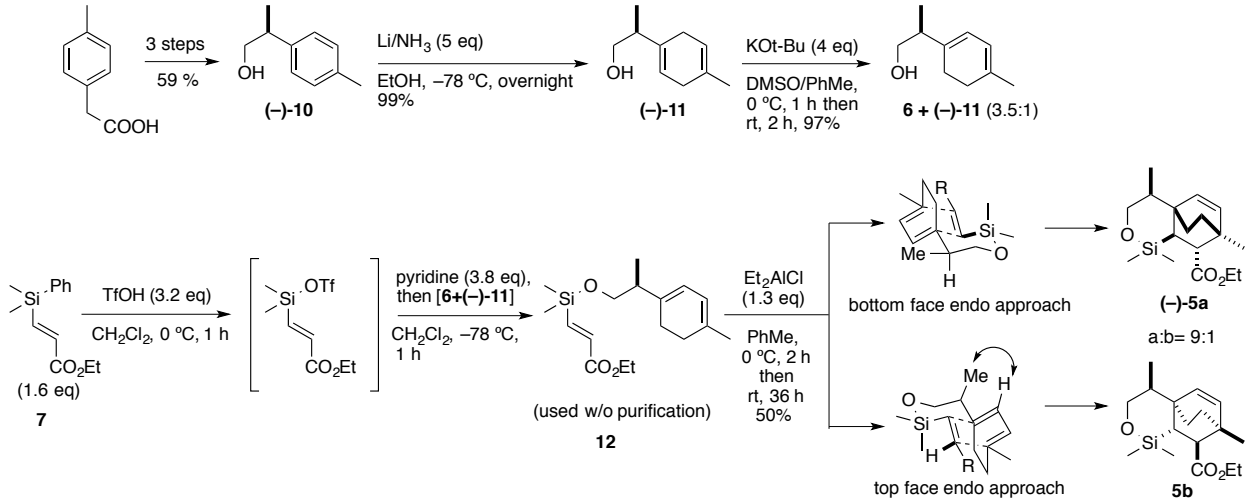
•**12**->**5**: Stereoselectivity in intramolecular Diels-Alder reaction

Dienophile favors *endo* approach from bottom face of diene π system.

- Endo approach from the bottom face => Alleviate $A^{1,3}$-strain interaction

-Endo selectivity=>Lowering the LUMO energy of the dienophile and greater secondary orbital interaction

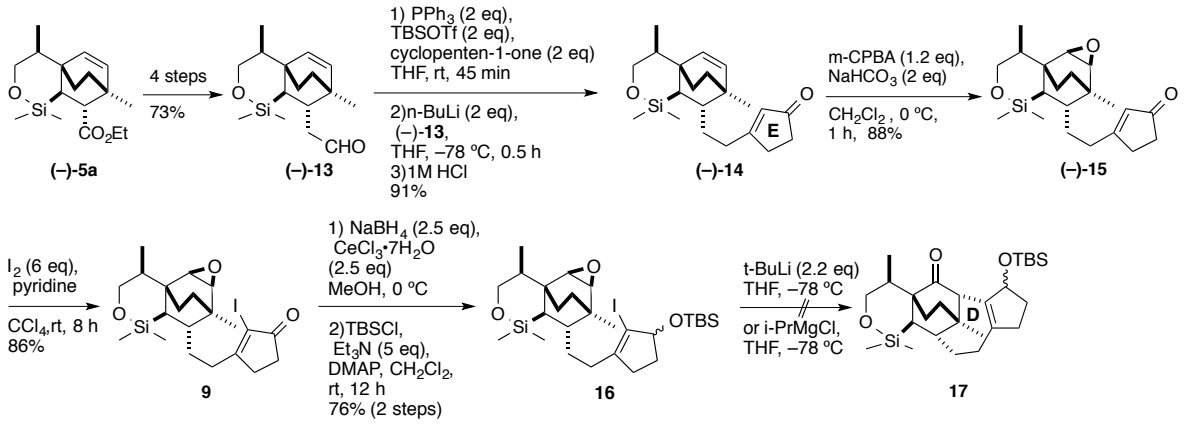
Scheme 1. Synthesis of bicyclic ester (–)-**5**



2-2. Construction of Ring D via epoxide

•Trial to attack ring E with organometal=> Metal-halogen exchange exclusively

Scheme 2. Cyclization of **16**.



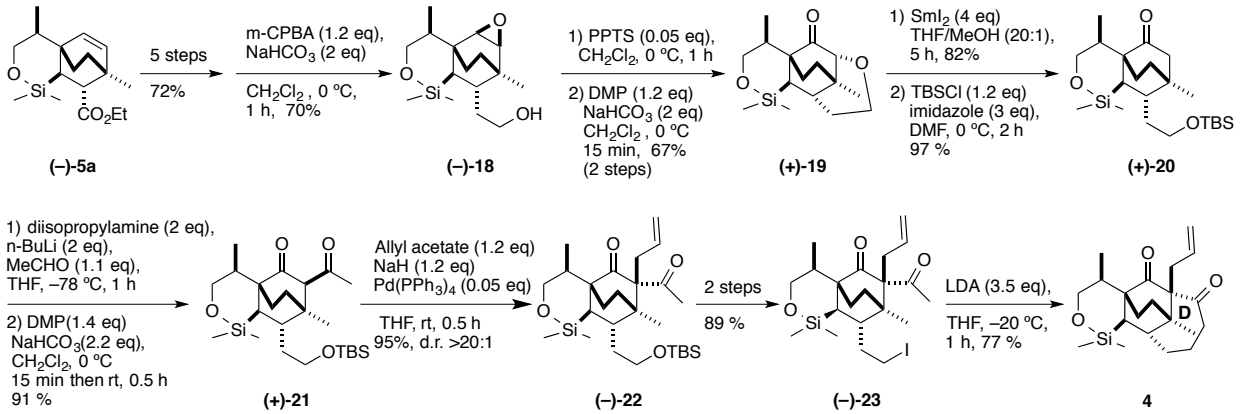
•Changing a strategy to construct ring D first

•**5a**->**18**: Epoxidation occurs from the top face because of the steric hindrance of a methyl.

•**20**->**21**: Steric hindrance of TBS=> MeCHO attacks from the top face.

•**21**->**22**: Because of soft nucleophilicity of **21**, it attacks allyl acetate from the top face.

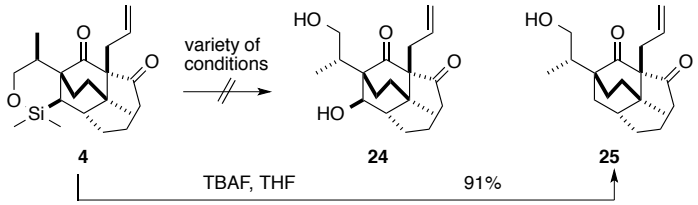
Scheme 3. Formation of ring D via epoxide.



2-3. Formation of Ring E

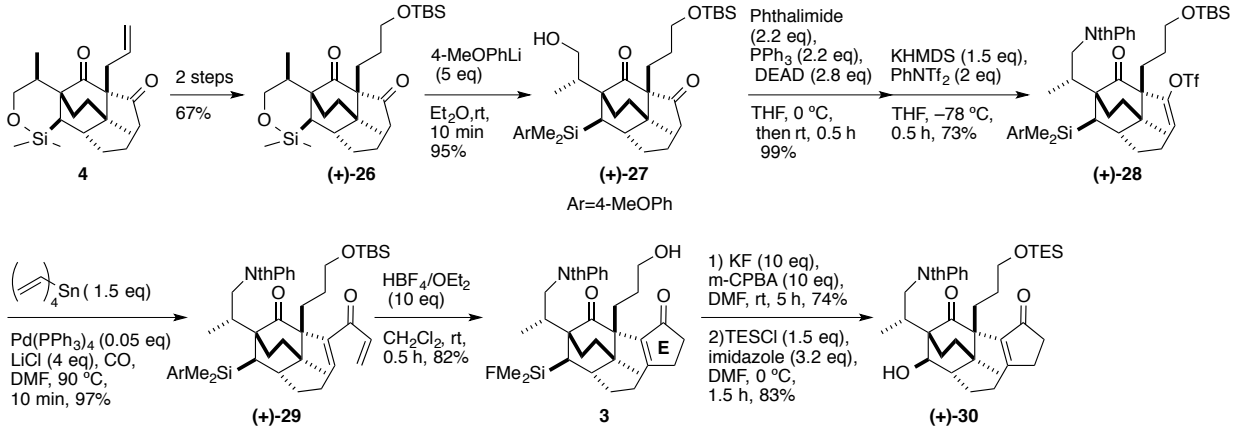
- Typical conditions (H_2O_2, m-CPBA)=> resistant to oxidation
- TBAF treatment=> **25**

Scheme 4. Attempted Tamao-Kumada oxidation.



- **26**->**27**: Siloxane ring opening with a strong carbon nucleophile
- **28**->**29**: Stille carbonylation to provide Nazarov precursor
- **29**->**3**: E ring construction by one-pot Nazarov cyclization and protodesilylation following Fleming-Tamao oxidation

Scheme 5. Construction of ring E.



2-4. Formation of Ring F and total synthesis of (–)-Calyciphylline-N

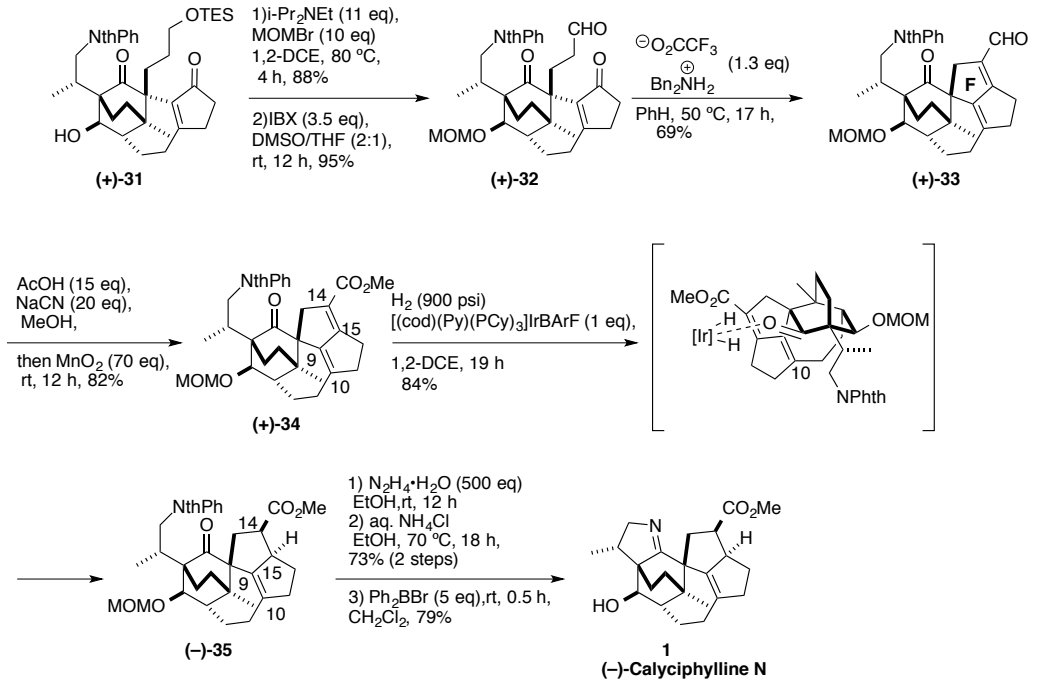
- **32**->**33**: Formation of ring F via aldol reaction

•**34**->**35**: Hydrogenation with Crabtree's catalyst with H_2 gas

-Coordination of the Ir catalyst to the carbonyl because of the decreased steric congestion

-Syn-hydrogenation to C14-C15 due to larger positive charge at C15

Scheme 6. Synthesis of ring F.



3. Conclusion

•(–)-Calyciphylline-N was obtained in overall 0.2% yield with 40 longest linear steps from the commercially available *p*-tolyacetic acid.

•Bicyclic core was constructed via intramolecular Diels-Alder reaction and Ring E was completed via Nazarov cyclization and Fleming-Tamao reaction.

4. Reference

1. Kobayashi, J. *et al*. *J. Nat. Prod.* **2008**, 72, 148., 2. Lu, Z. *et al. Nat. Chem.* **2013**, 5, 679.

3. Darses, B. *et al. Org. Lett*. **2012**, 14, 1684.

5. Appendix