Literature Report (11)

Total Synthesis of Rubriflordilactone B

Reporter: Yue Ji
Checker: Mu-Wang Chen
Date: 2016/12/26

Yang, P.; Yao, M.; Li, J.; Li, Y.; Li, A.* *Angew. Chem. Int. Ed*. **2016**, *55*, 6964.

Laboratory of Asymmetric Catalysis, 201

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- Asymmetric Total Synthesis of Rubriflordilactone B
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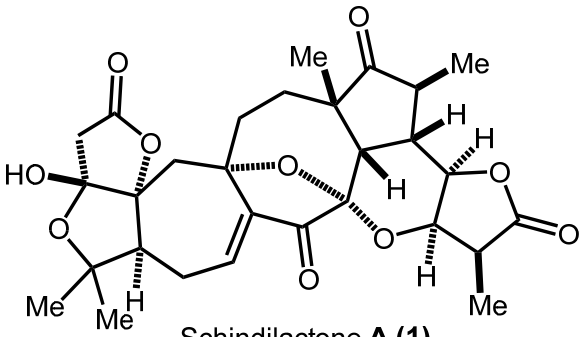
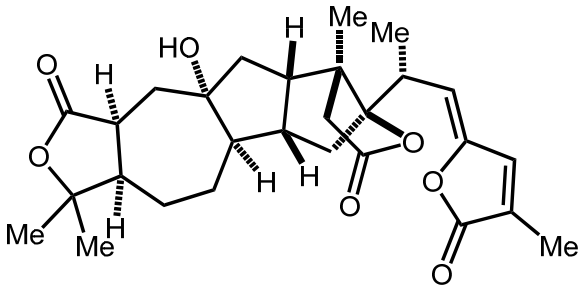
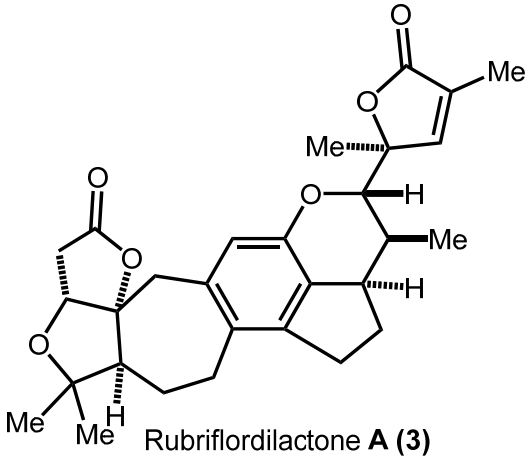
Introduction



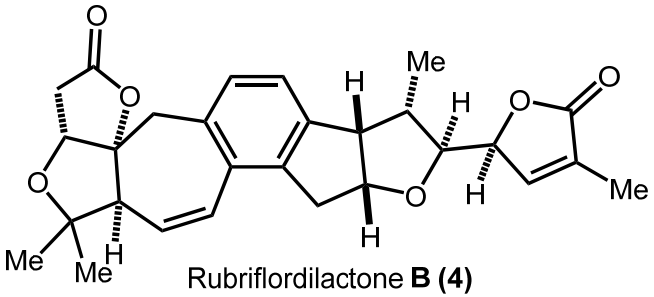
Schindilactone **A (1)**



Schilancitrilactone **B (2)**



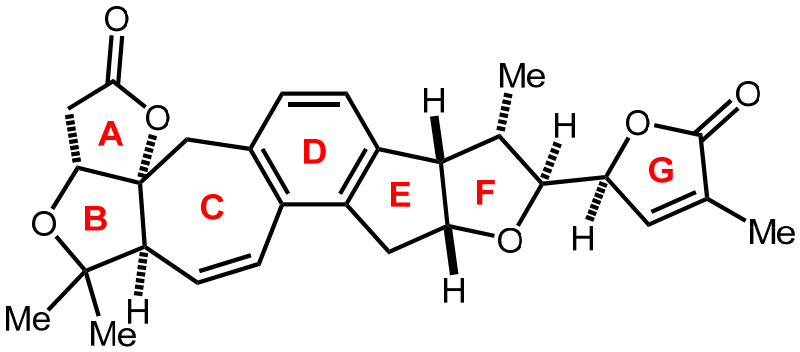
Rubriflordilactone **A (3)**



Rubriflordilactone **B (4)**

Sun, H.-D. *et al. Org. Lett.* **2006**, *8*, 991.
Sun, H.-D. *et al. Nat. Prod. Rep.* **2008,** *25*, 871.

Introduction



Rubriflordilactone B (4)

Schisandra rubriflora

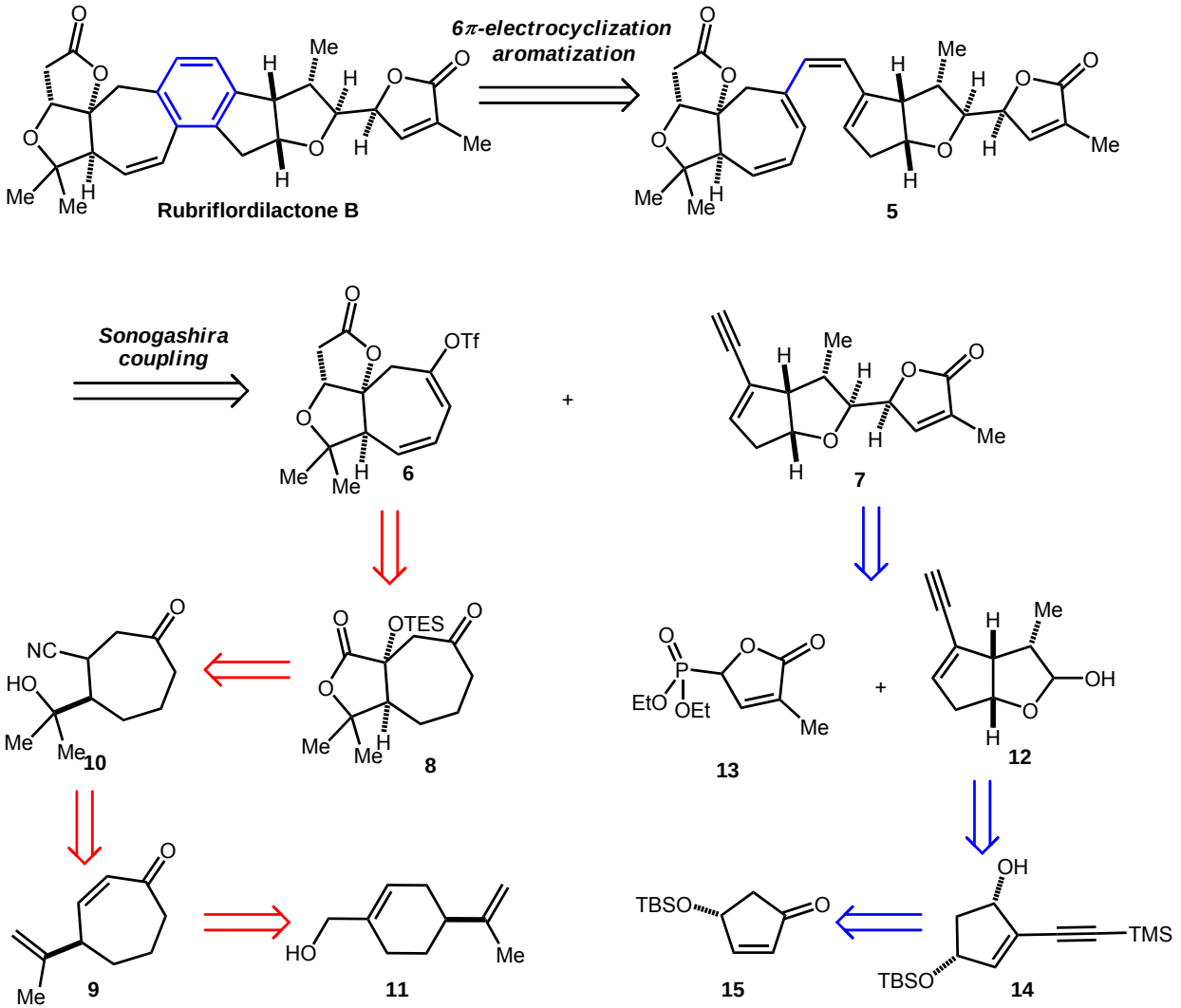
Biological activity: an EC_{50} value of 9.75 ug/mL against HIV-1 replication with low cytotoxicity

Structure features: a heptacyclic bisnortriterpenoid backbone, 8 stereogenic centers, 5 contiguous chiral centers, a seven membered ring, a tetrasubstituted arene moiety

https://en.wikipedia.org/wiki/Schisandra

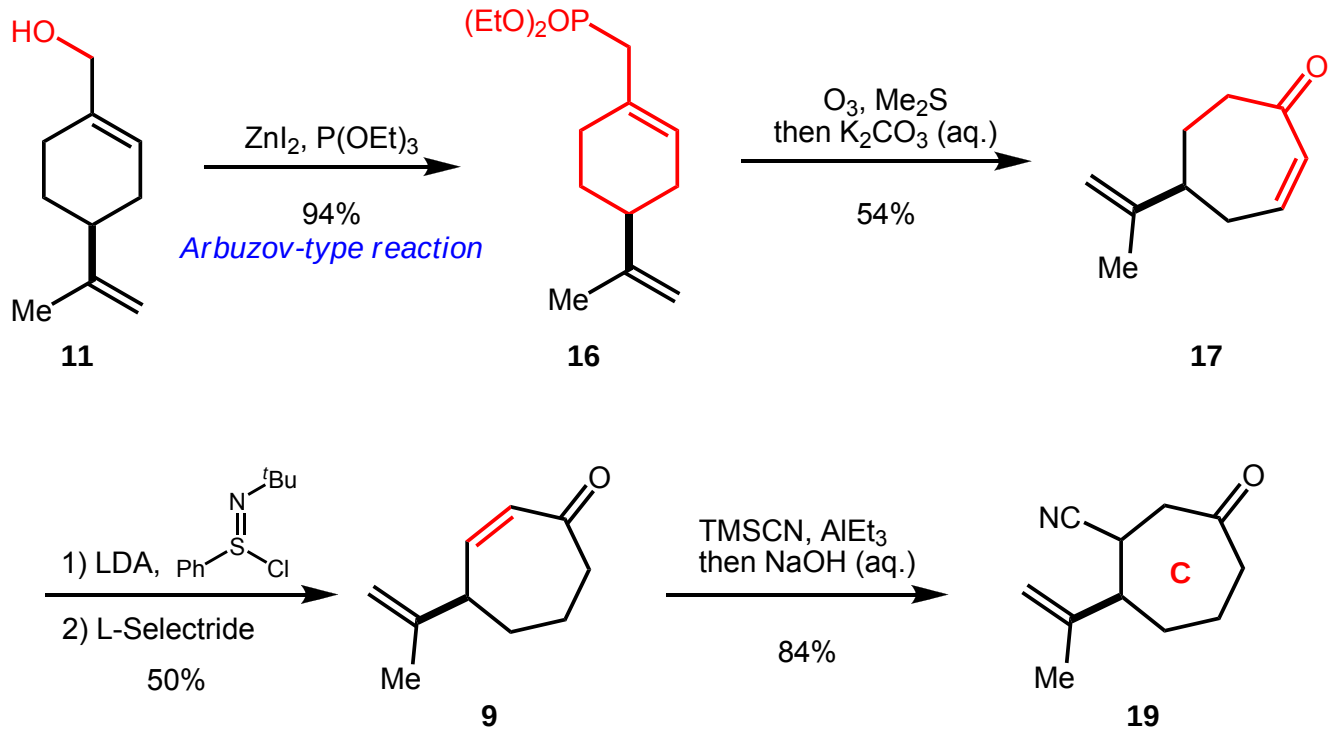
Sun, H.-D. *et al. Org. Lett.* **2006**, *8*, 991.

Retrosynthetic Analysis of Rubriflordilactone B

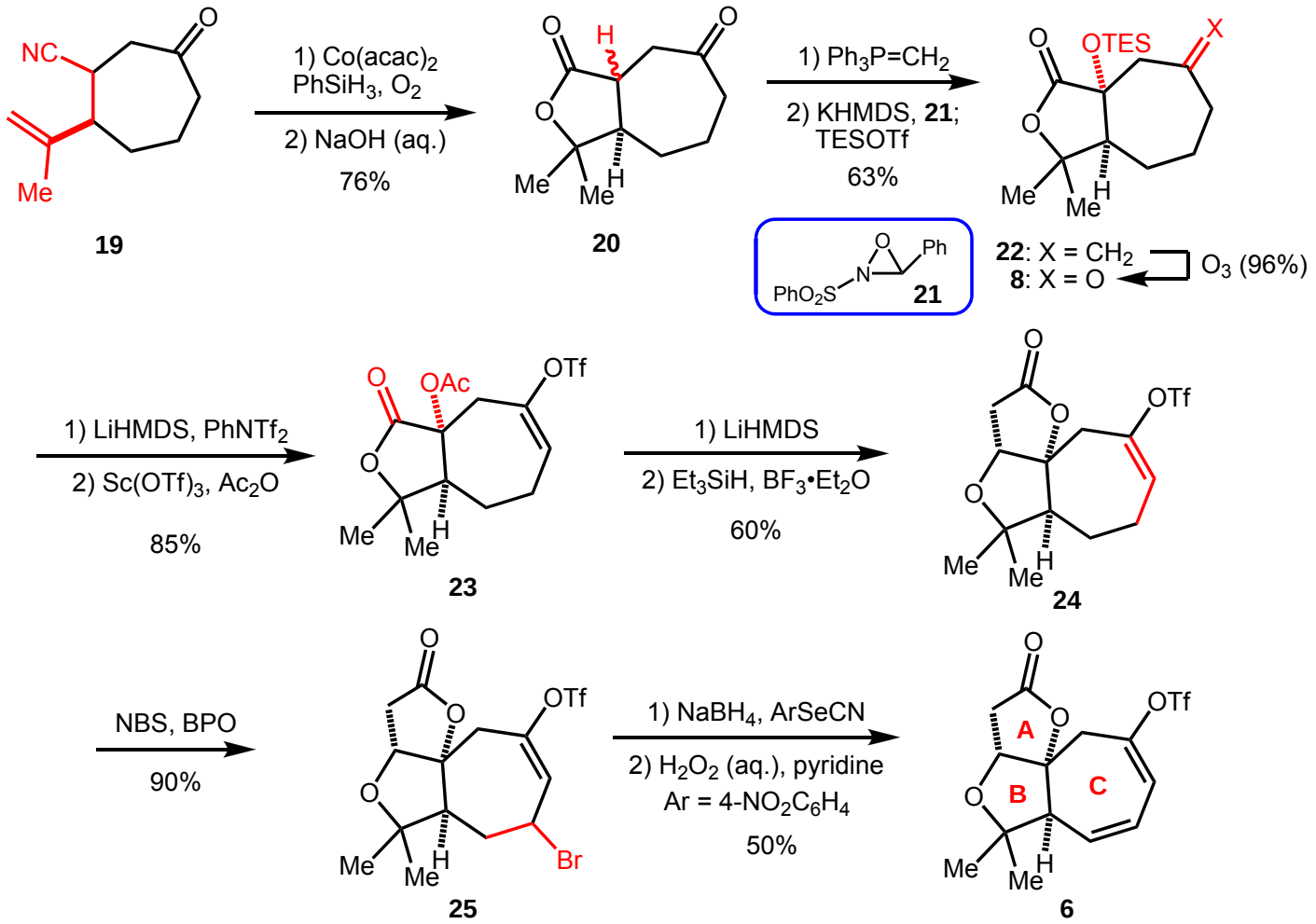


Li, A. *et al. Angew. Chem. Int. Ed*. **2016**, *55*, 6964.

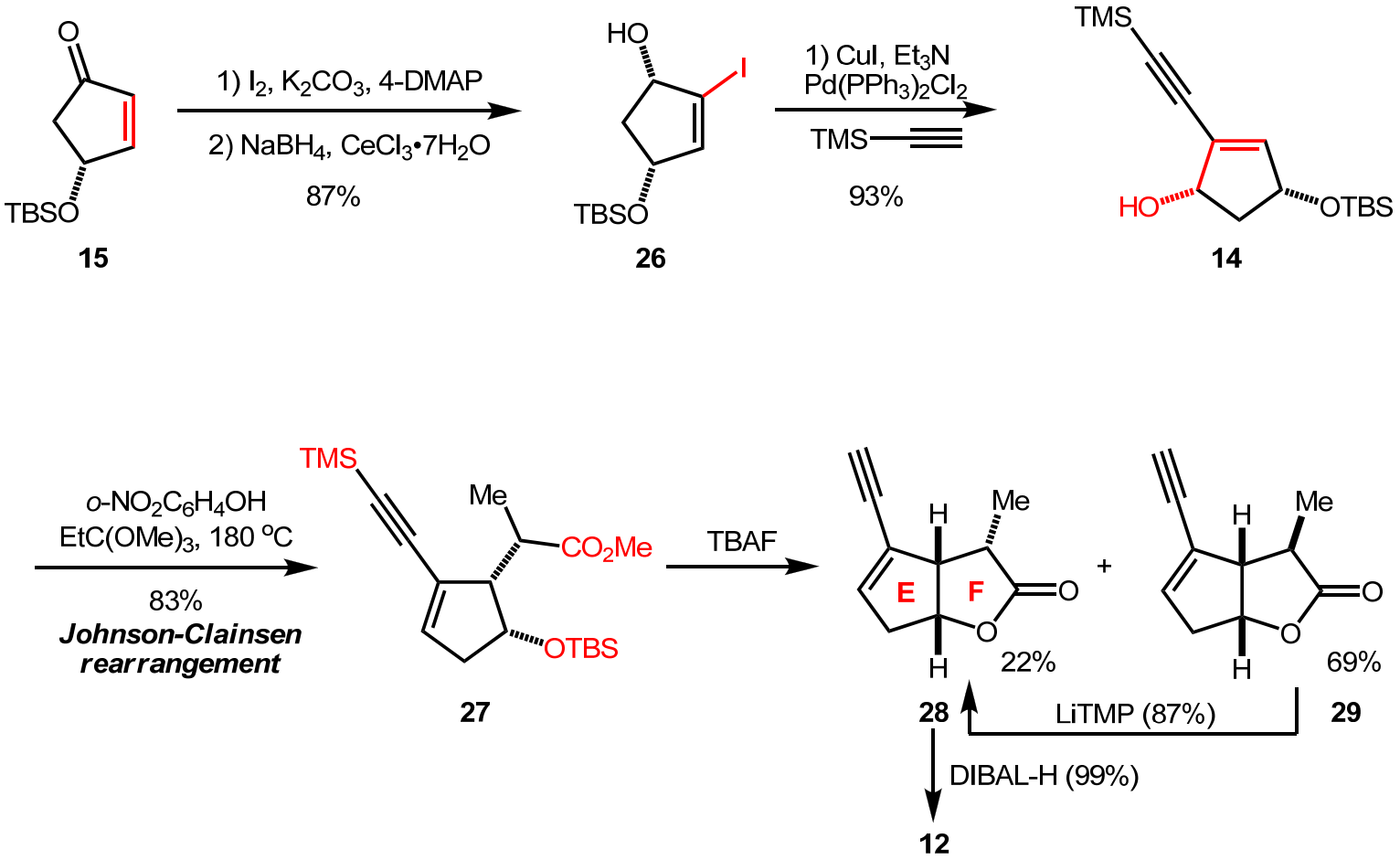
Synthesis of the left-hand fragment



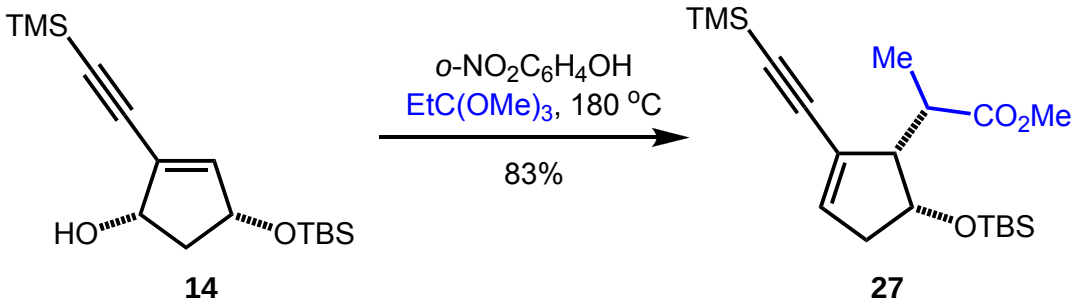
Synthesis of the left-hand fragment



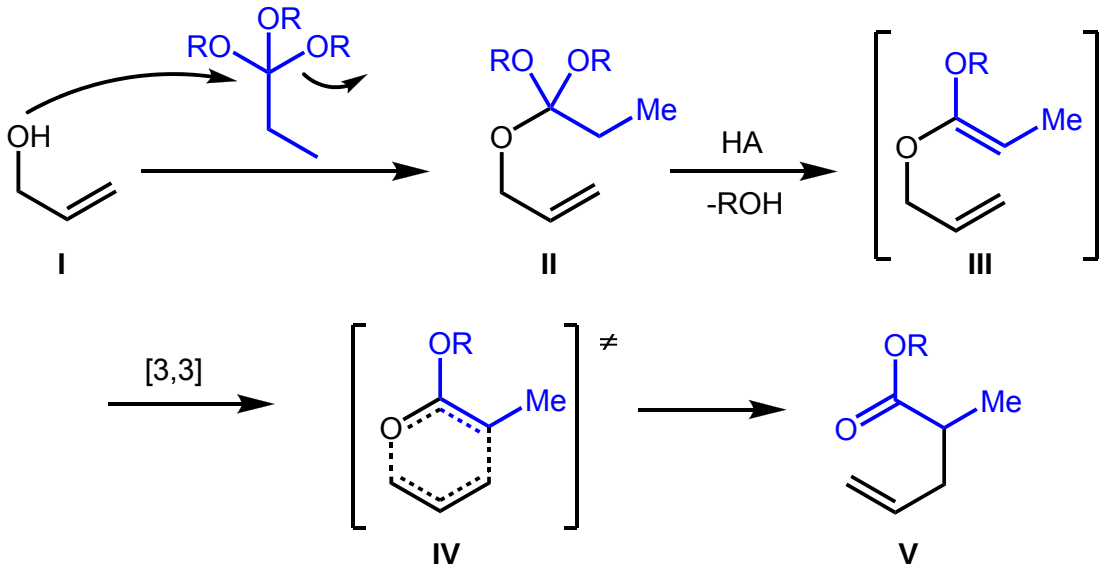
Synthesis of the right-hand fragment



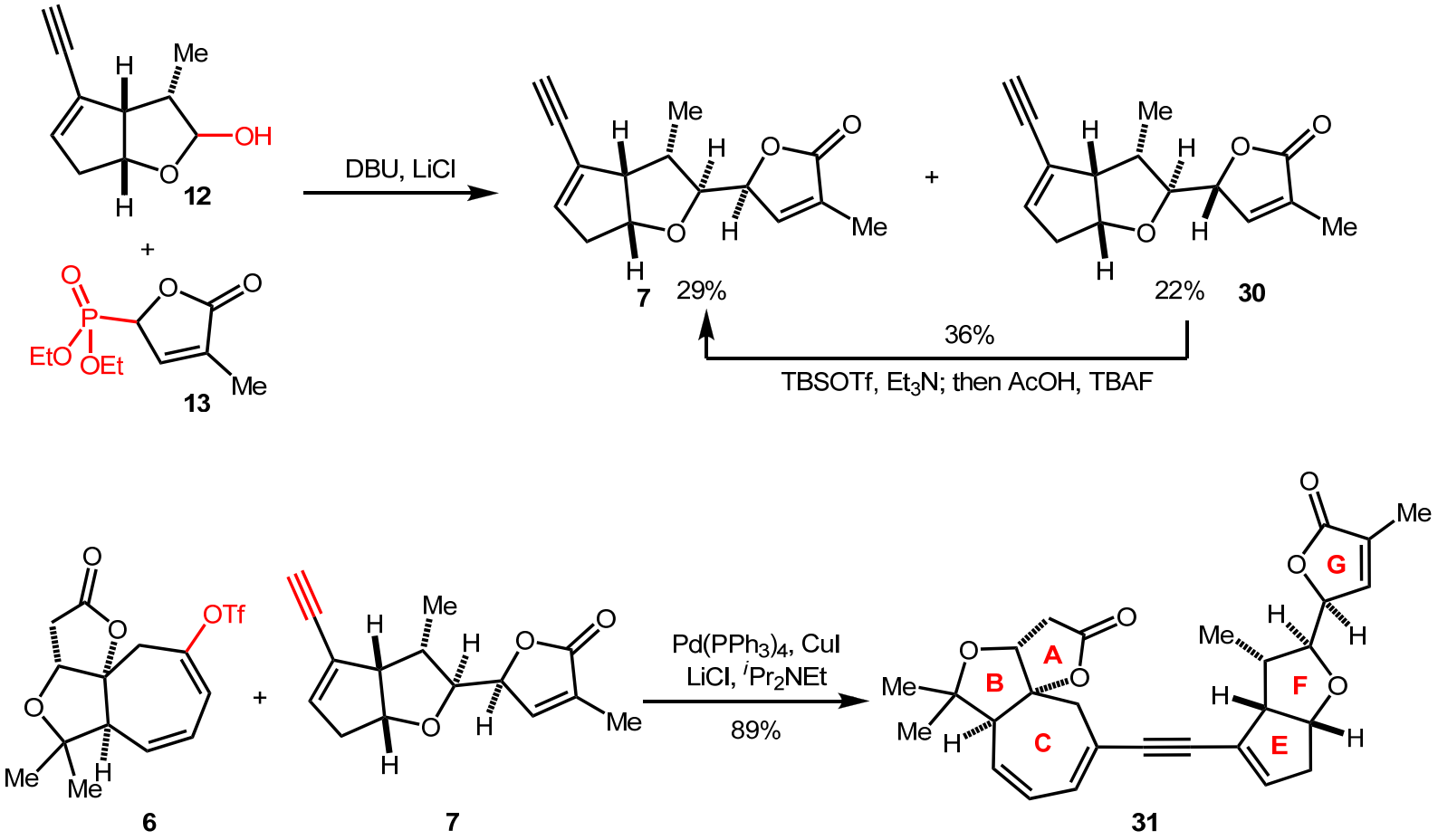
Johnson-Claisen rearrangement



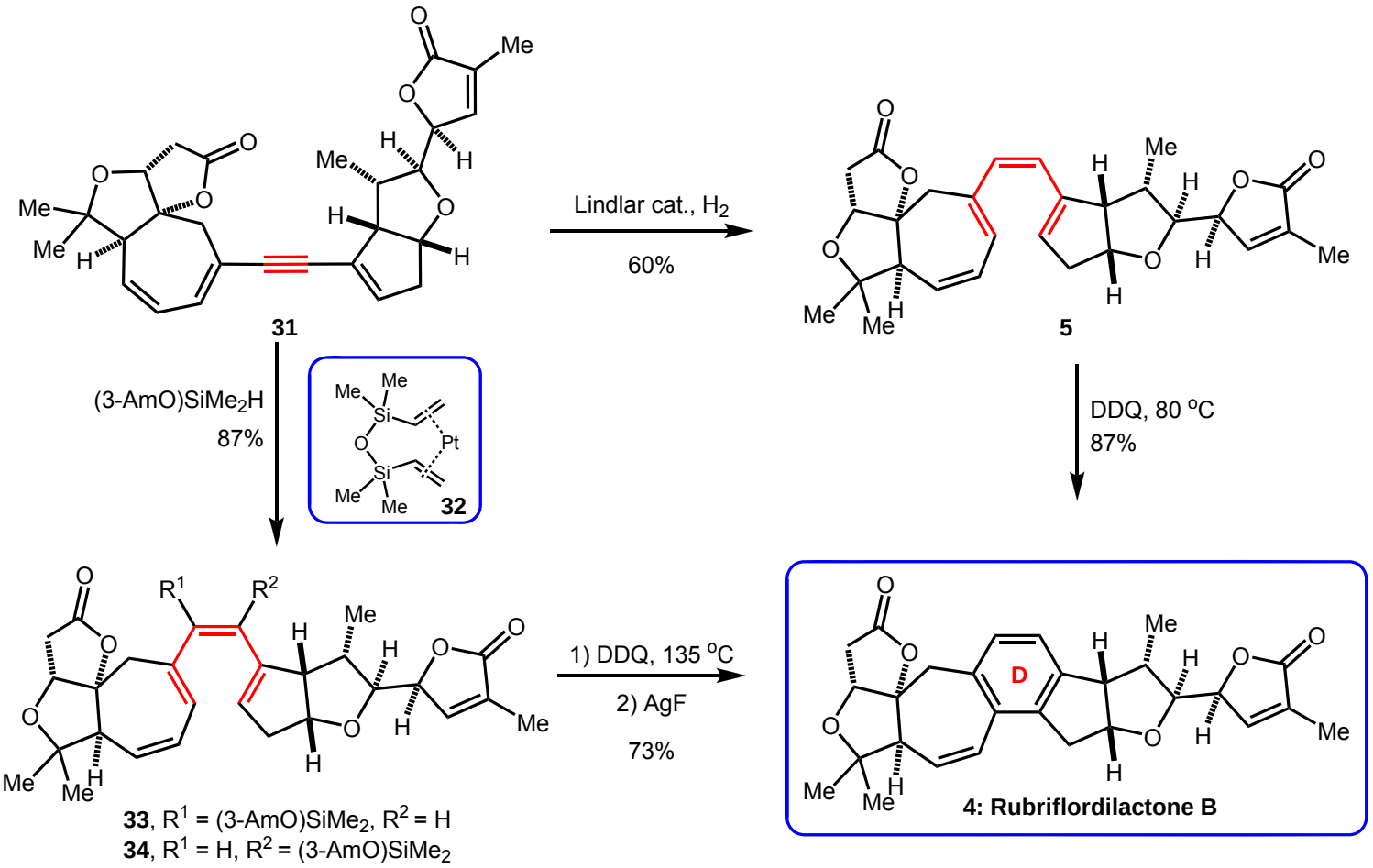
Mechanism:



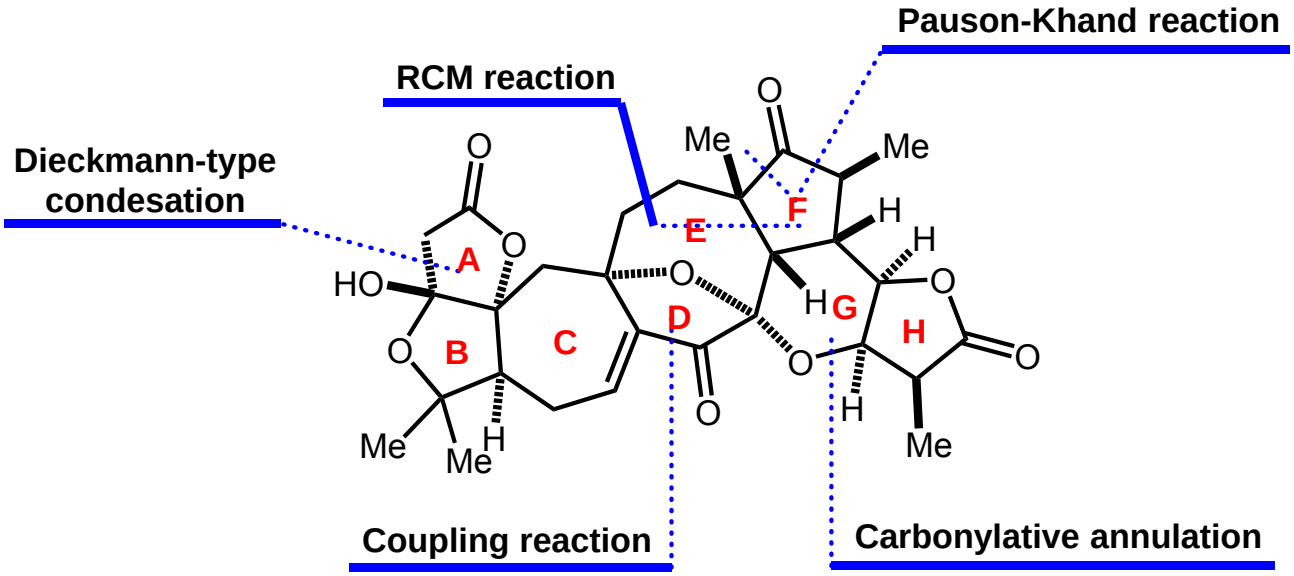
Asymmetric Total Synthesis of Rubriflordilactone B



Asymmetric Total Synthesis of Rubriflordilactone B



Total Synthesis of (+/-)-Schindilactone A



Schindilactone A (1)

Structure features: a highly oxygenated octacyclic framework bearing 12 stereogenic centers, 8 contiguous chiral centers, an oxa-bridged ketal that lies within an unprecedented fused core.

Sun, H.-D. *et al. Nat. Prod. Rep.* **2008,** *25*, 871.

Tang, Y.-F.; Chen, J.-H.; Yang, Z. *et al*. *Angew. Chem. Int. Ed.* **2011**, *50,* 7373.

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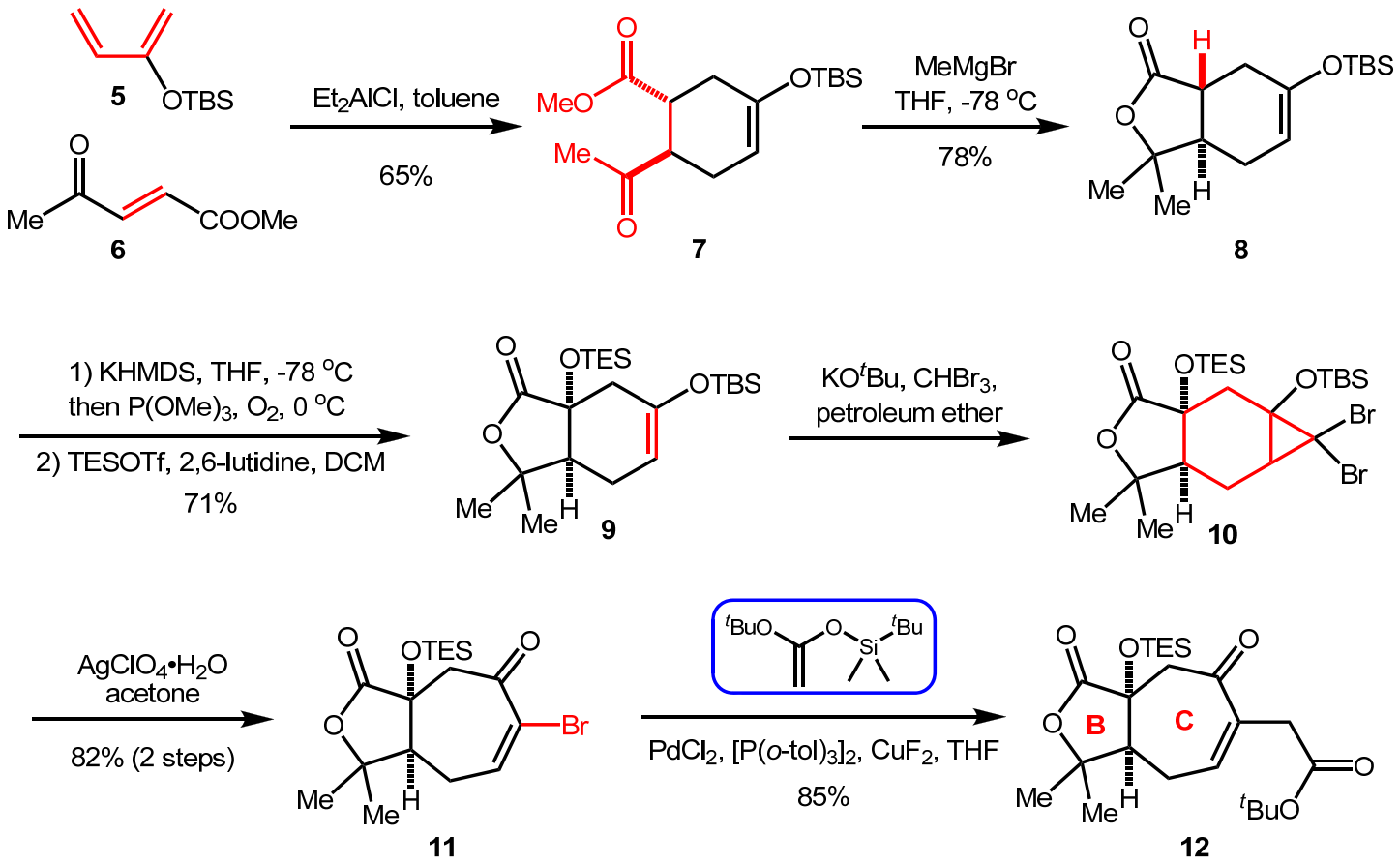

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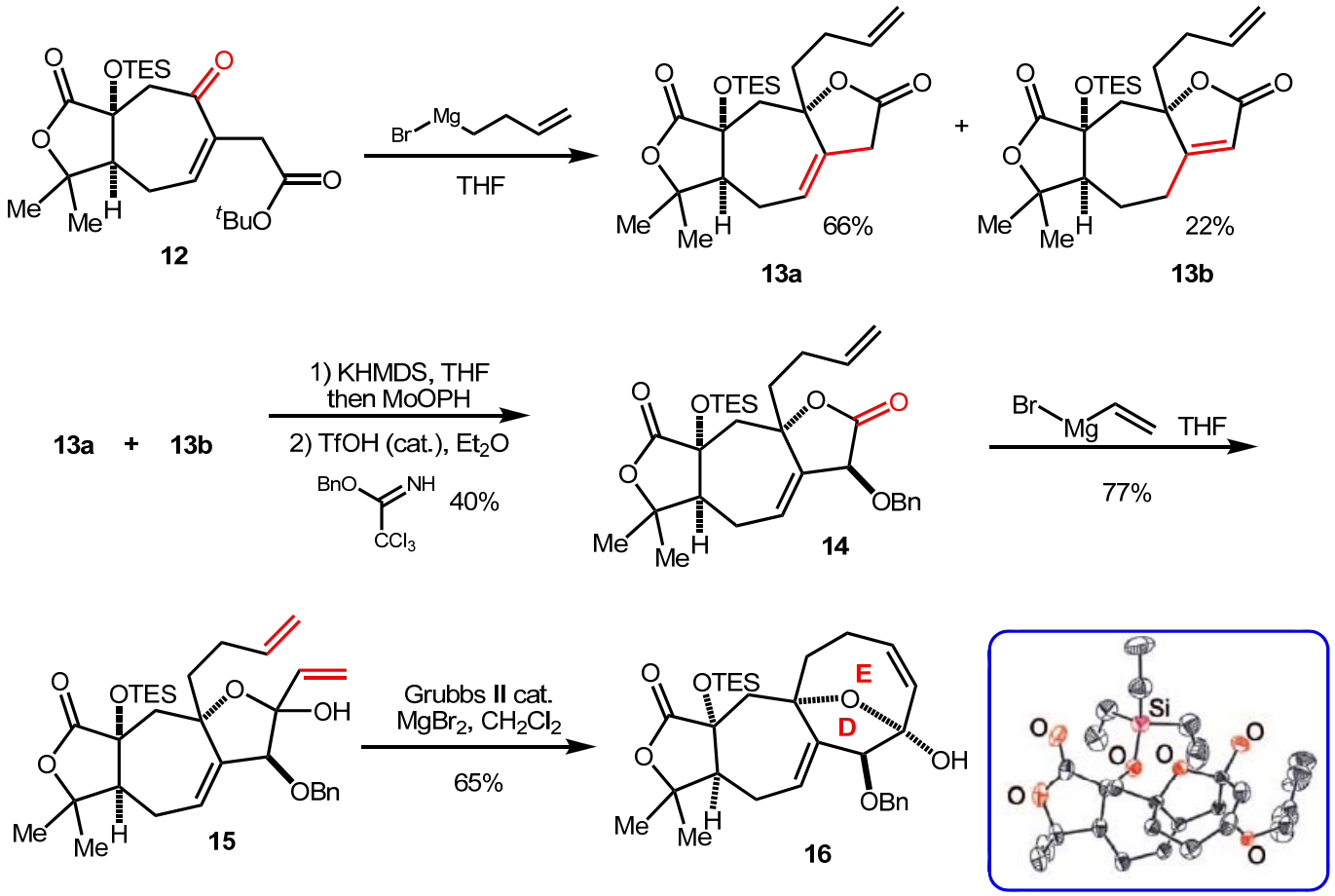
Total Synthesis of (+/-)-Schindilactone A



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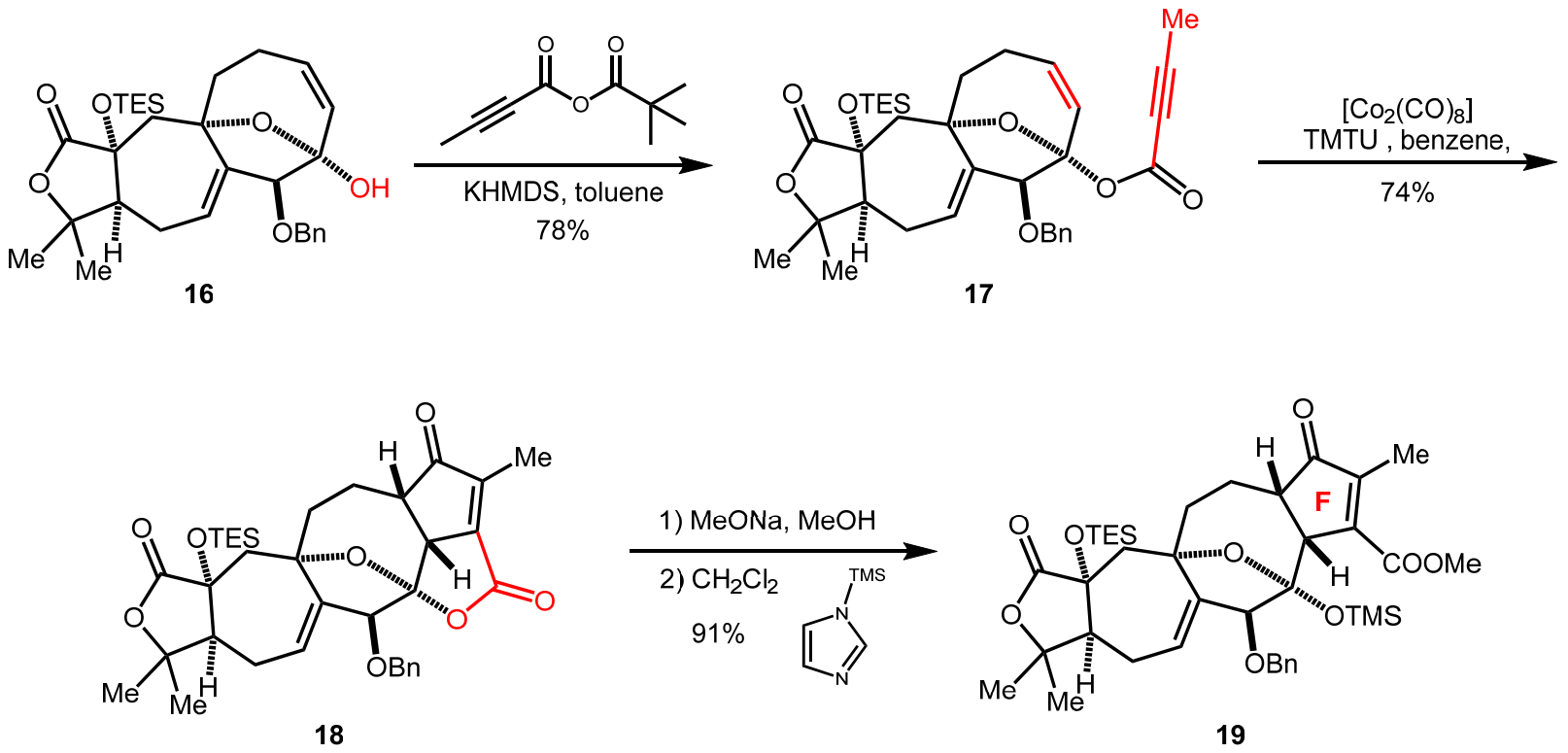
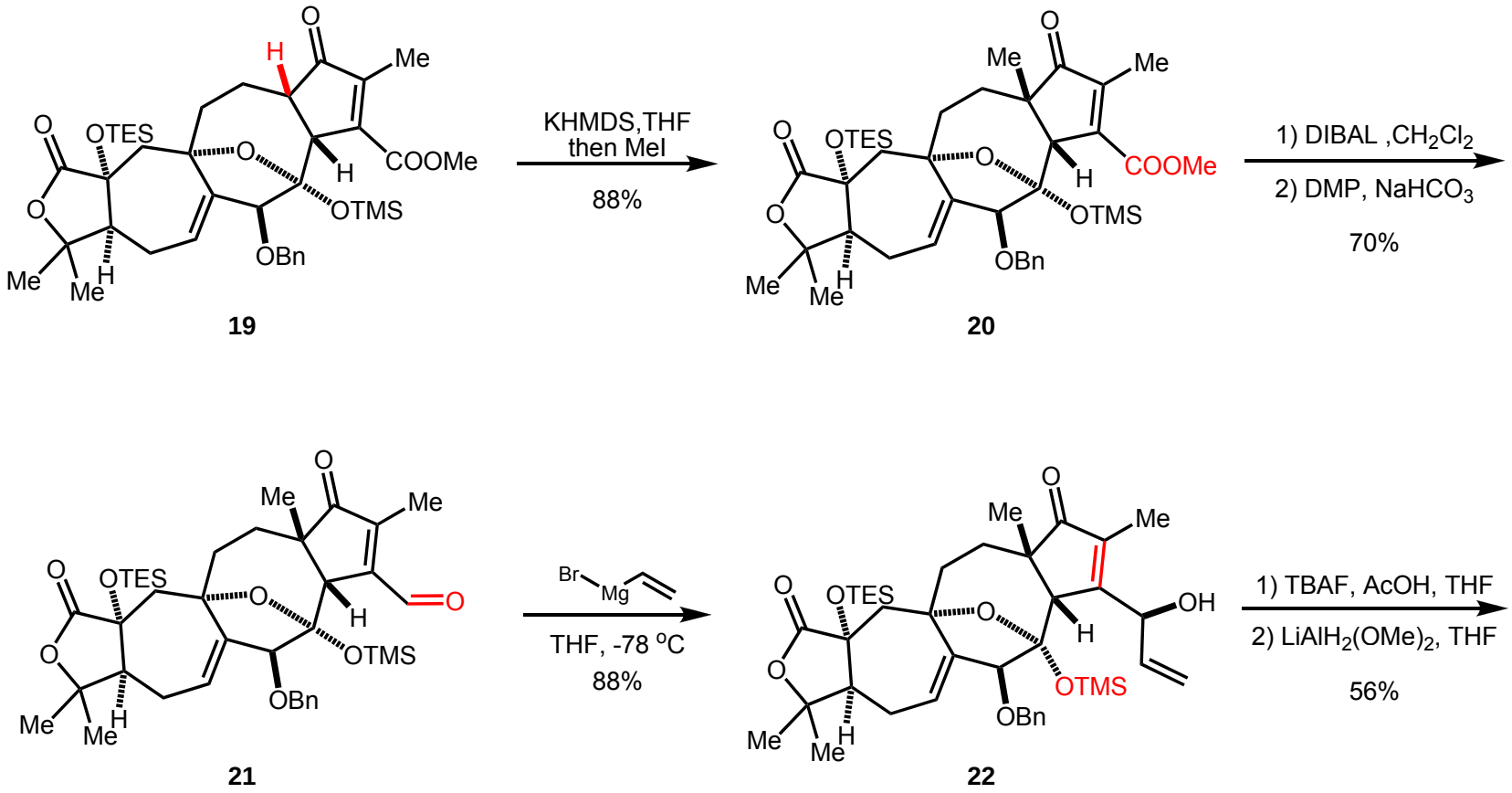


Total Synthesis of (+/-)-Schindilactone A



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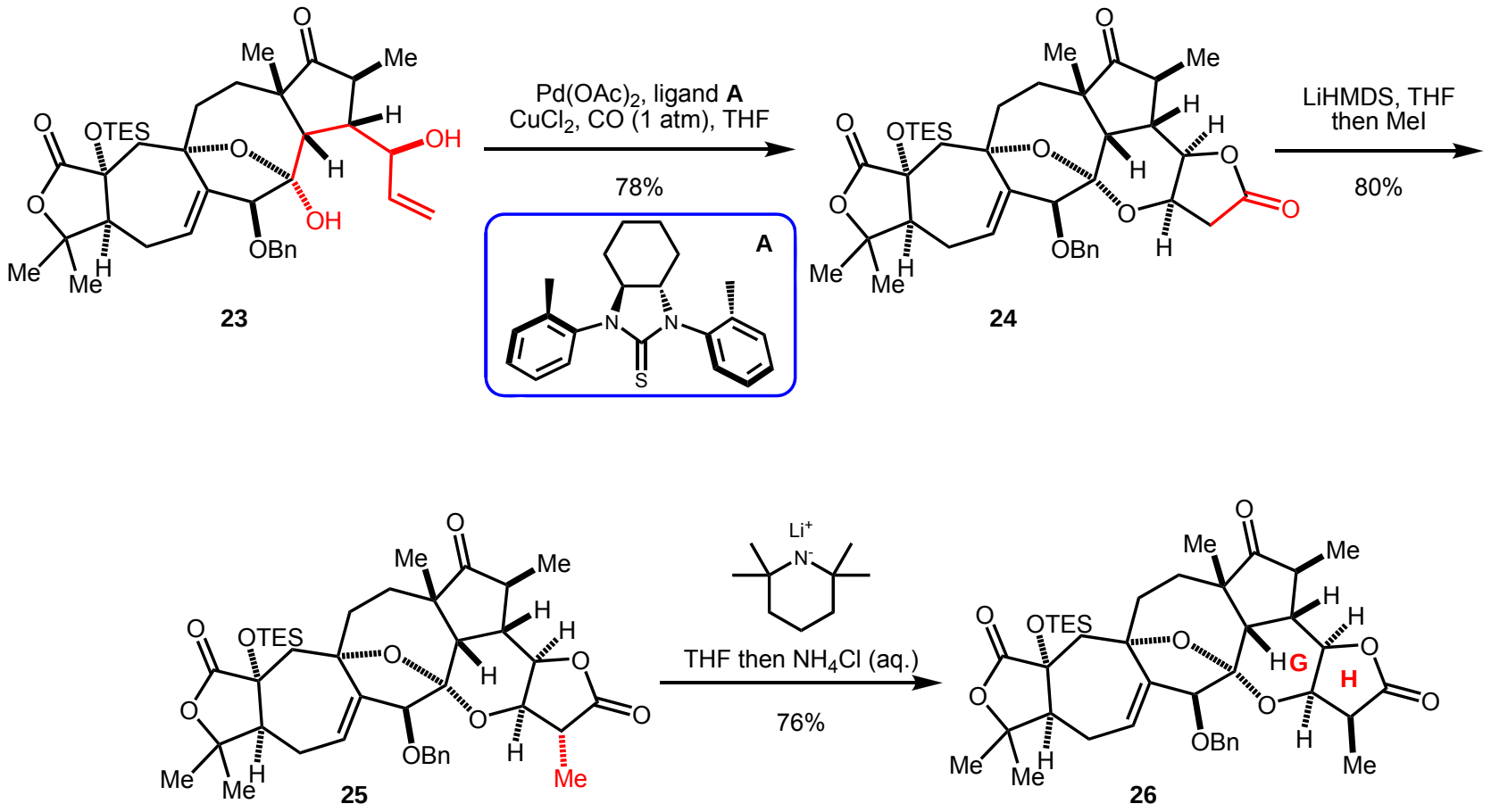
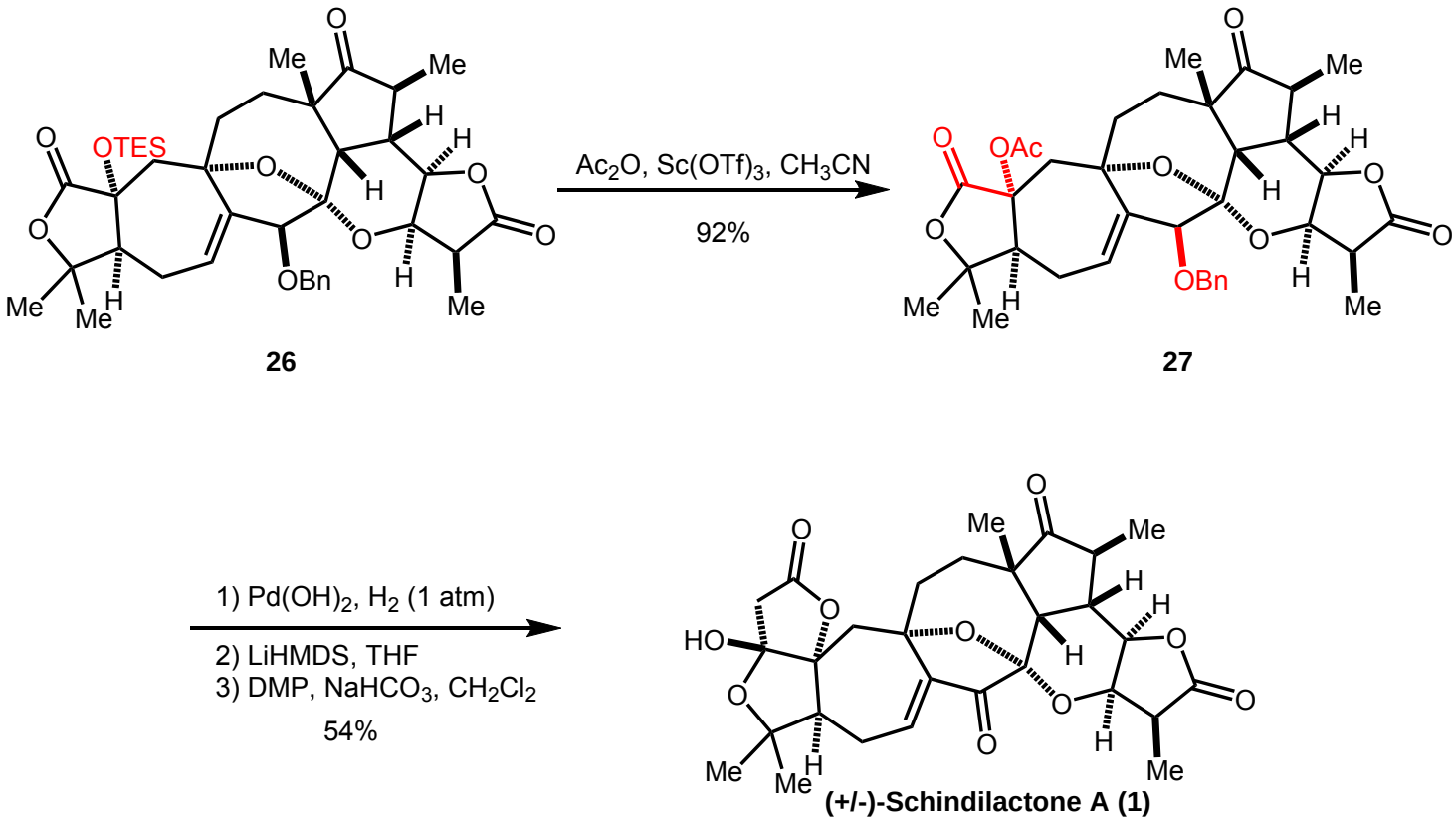


Total Synthesis of (+/-)-Schindilactone A



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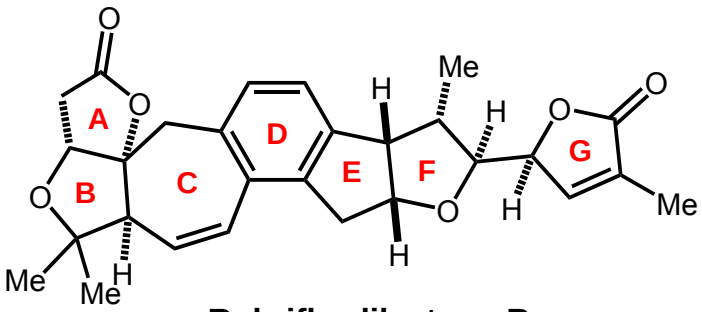
(+/-)-Schindilactone A (1)

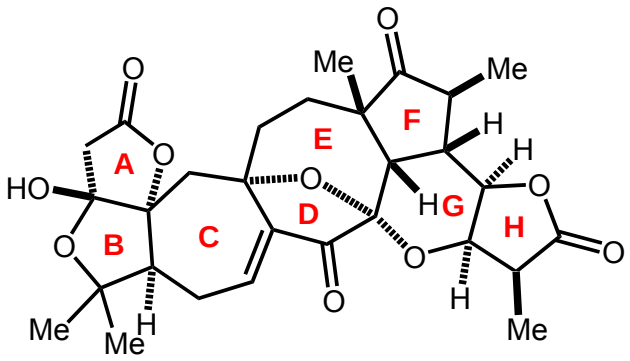
Summary



Rubriflordilactone B

Li's work

1. **Asymmetric total synthesis, 20 steps, 0.20% yield**
2. **Highly convergent strategy for total synthesis**
3. **Sonogashira-hydrosilylation-electrocyclization-aromatization sequence for pentasubstituted arenes**



Schindilactone A

Yang's work

1. **Racemic total synthesis, 29 steps, 0.17% yield**
2. **Silver-mediated cyclopropane rearrangement to generate the C ring**
3. **RCM reaction for the formation of the fully functionalized eight-membered E ring**
4. **Thiourea/cobalt-catalyzed PKR for the F ring**
5. **Thiourea/palladium-catalyzed carbonylative annulation for GH ring**

Constructing multisubstituted arenes remains a challenge in natural product synthesis. Conventional strategies based on substitution-type reactions, such as Friedel–Crafts, S_N2Ar, and cross-coupling reactions, are limited by the availability and electronic properties of the corresponding substrates and the positional selectivity of these transformations, despite being recently reinforced by transition-metal- or radical-mediated C-H bond functionalization. The groups of Nicolaou and others have elegantly demonstrated the power of electrocyclization in natural product synthesis. The combination of 6π electrocyclization and oxidative aromatization for constructing multisubstituted arenes is of significant advantage from the following aspects: 1) strong driving force, 2) no functionalization (e.g., halogenation or metalation) required, 3) separating stereochemical problems from connectivity issues, 4) eliminating torquoselectivity issues, and 5) enhanced convergence.

Thus, such strategies were creatively applied by a number of groups in synthesizing natural products containing multisubstituted arenes, which recently inspired us to explore this area. However, the geometrically controlled formation of the prerequisite triene substrates is a considerable challenge for executing the electrocyclization strategy. Partial-hydrogenation reagents (e.g., Lindlar catalyst, diazene, activated Zn) suffer from incompatibility issues with functionalized diene-ynes and result in poor yields of the desired cis-trienes. Precursors of penta- and hexasubstituted arenes pose even greater difficulties in controlling the geometry of the more substituted olefin substrates

In summary, we have accomplished the total synthesis of rubriflordilactone B in a highly convergent fashion. A 6π electrocyclization–aromatization sequence served as a key step. Hydrosilylation of a conjugated triene-yne intermediate defined the *cis* geometry of the electrocyclization precursor, which constitutes a superior approach to the conventional method of partial hydrogenation. The Sonogashira– hydrosilylation–electrocyclization –aromatization sequence could be streamlined as a general and robust approach towards the synthesis of pentasubstituted arenes bearing silyl groups as versatile handles, considering that the regioselectivity of the hydrosilylation can be tuned by varying the ligands. The total synthesis suggests the existence of a naturally occurring sibling of rubriflordilactoneB and provides efficient and flexible access to analogues of potential biological interest.