

Asymmetric Total Synthesis of Mycoleptodiscin A

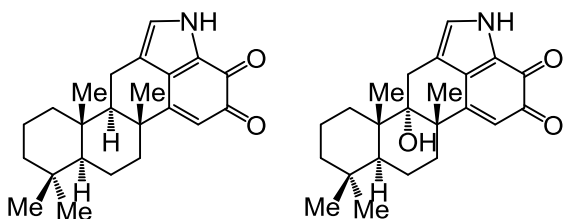
Shupeng Zhou, Hao Chen, Yijie Luo, Wenhao Zhang and Ang Li

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032 (China)

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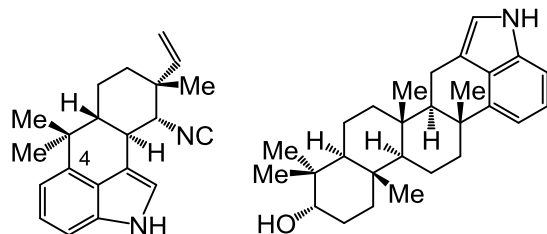
I. Introduction



1: mycoleptodiscin A 2: mycoleptodiscin B

- The isolation of Mycoleptodiscins A and B was reported in 2013.
- Compound **2** displays anti-cancer activity, while the biological activity of **1** was unknown, possibly due to its natural source scarcity.
- Chemical structural character: C-4 alkylated indole terpenoids, such as Hapalindole H (**3**) and petromindole (**4**).

II. Synthetic Considerations

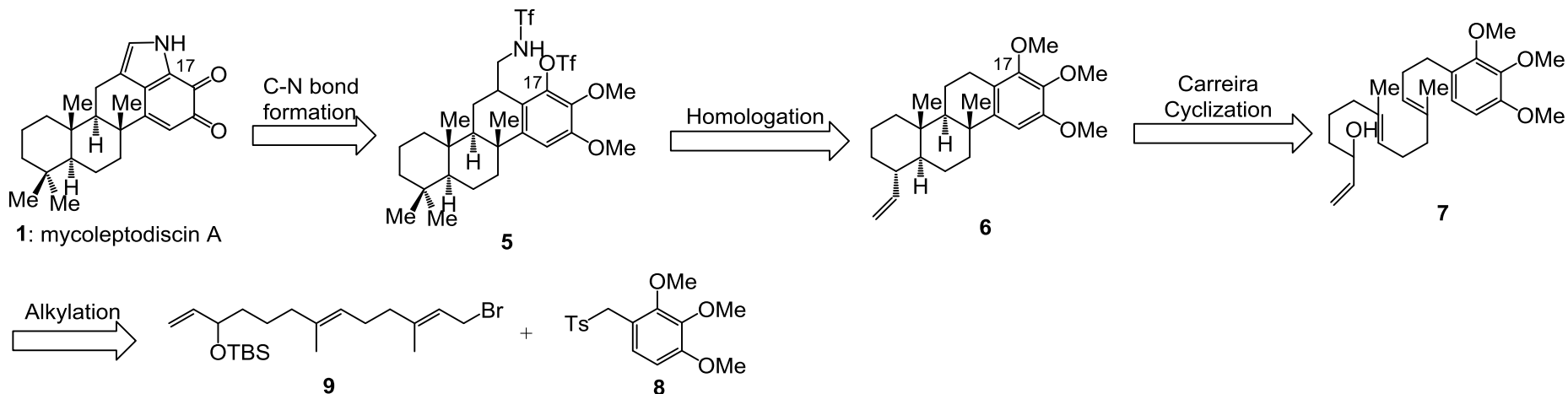


3: hapalindole H 4: petromindole

- Friedel–Crafts reaction to indole C4 alkylation is problematic because of the lower nucleophilicity at C-4 than that at C-2.
- Another alternative strategy such as reductive Heck annulation is also problematic. For the case of **1**, the unusual ortho-benzoquinone moiety makes difficulties to apply this strategy: preparation of 4-Br indole for reductive Heck reaction is non-trivial.
- Challenges in the synthesis of **1**: 1) assembly of the multisubstituted indole motif; and 2) construction of the sesquiterpenoid framework in an asymmetric way.

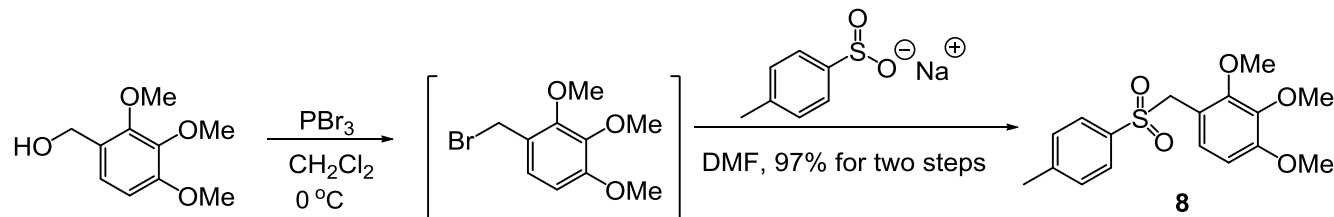
Total Synthesis of Mycoleptodiscin A

III. Retrosynthetic Analysis



- The enantioselective synthesis of **6** will be the key step.
- Carreira cyclization, which was reported in 2012, has emerged as a powerful synthetic method in natural product total synthesis. This Iridium-catalyzed enantioselective polyene cyclization was used to construct bi- and tricyclic systems. Carreira only described one example of tetracycle cyclization reaction.
- The indole ring was assembled by transition-metal catalyzed aryl amination reaction at C-17 position.

IV. Synthesis

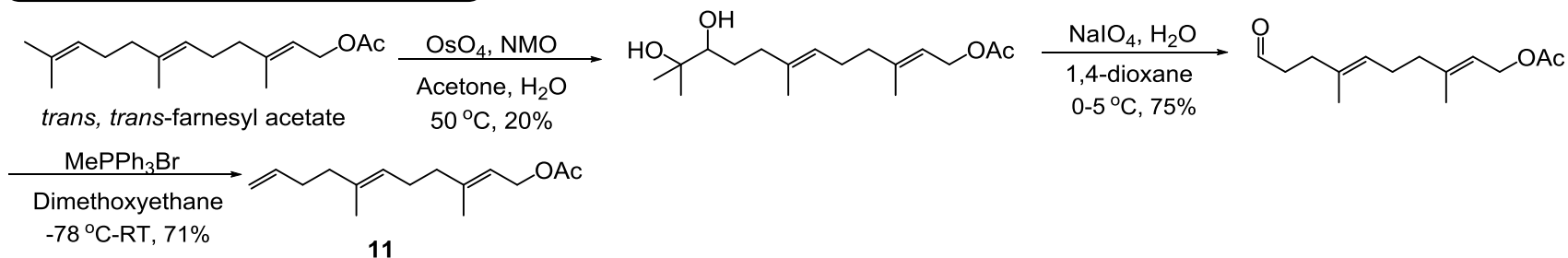


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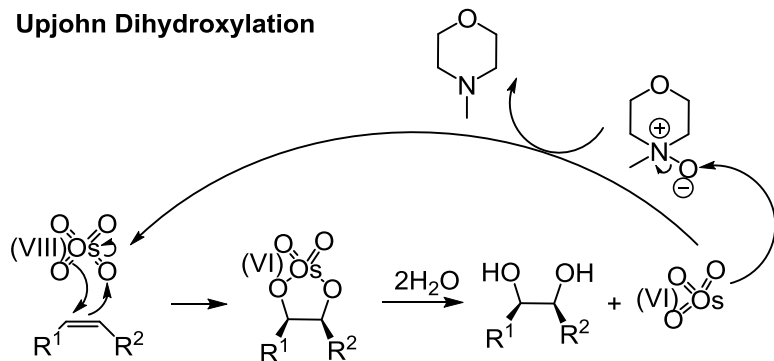
G. Evano, J. V. Schaus, J. S. Panek, *Org. Lett.* **2004**, *6*, 525.

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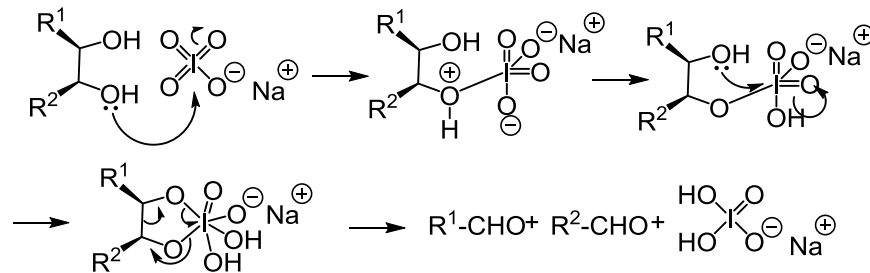
IV. Synthesis



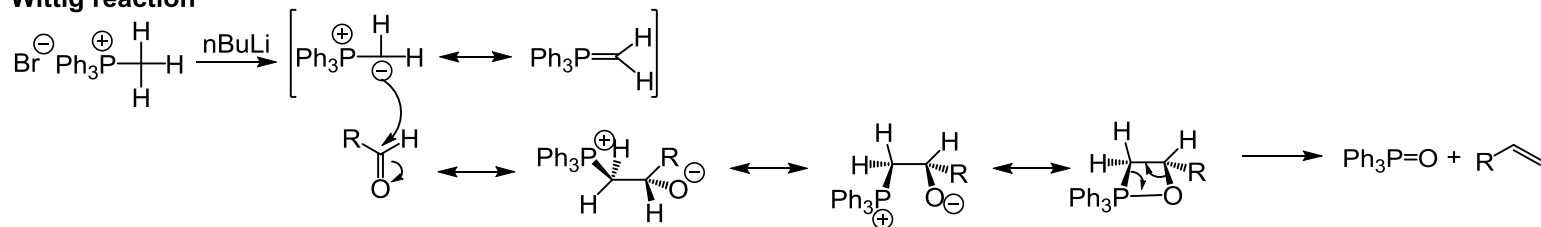
Upjohn Dihydroxylation



Sodium periodate oxidation



Wittig reaction

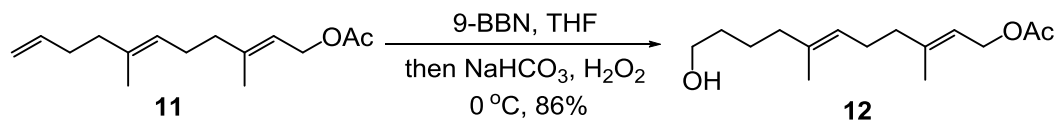


S. Yildizhan, J. van Loon, A. Sramkova, M. Ayasse, C. Arsene, C. ten Broeke, S. Schulz, *ChemBioChem* **2009**, *10*, 1666.

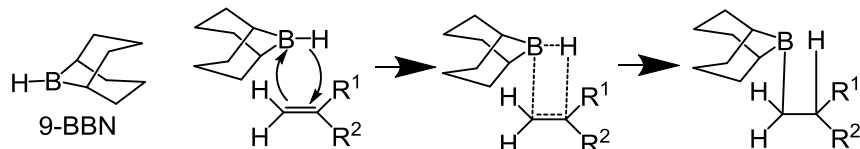
Total Synthesis of Mycoleptodiscin A

IV. Synthesis

Construction of polyene 7 – Part 1

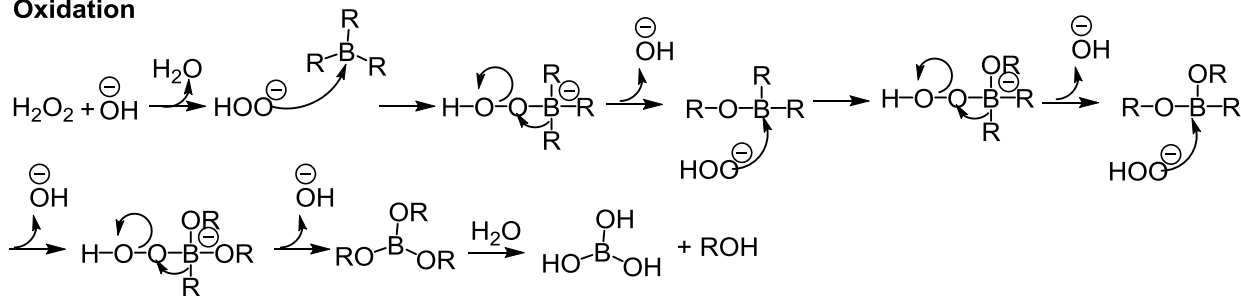


Hydroboration



syn-Addition; Selectivity: boron adds preferentially to the least hindered carbon. Sterically demanding 9-BBN has enhanced selectivity.

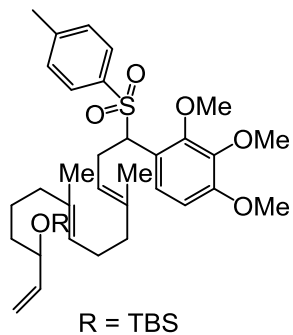
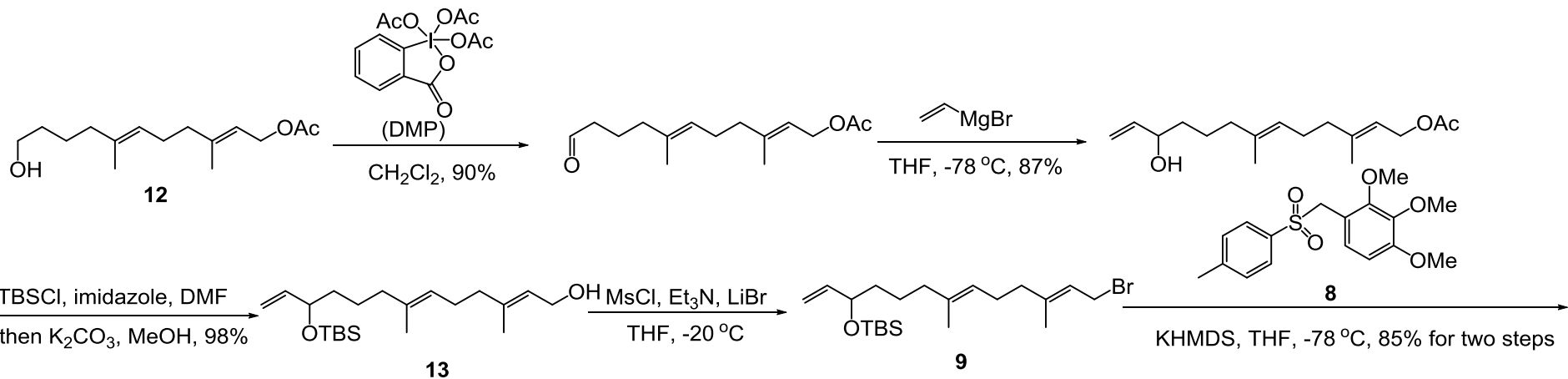
Oxidation



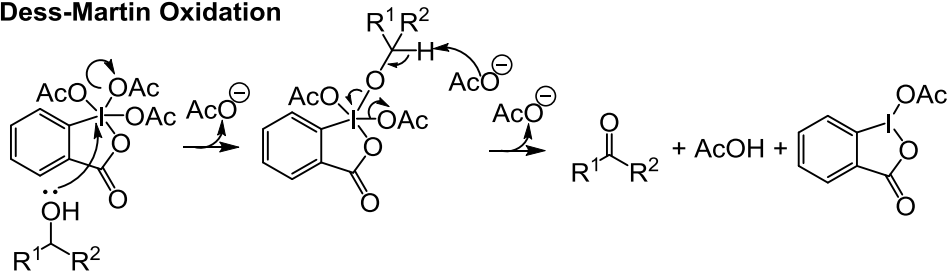
Total Synthesis of Mycoleptodiscin A

IV. Synthesis

Construction of polyene 7 – Part 2



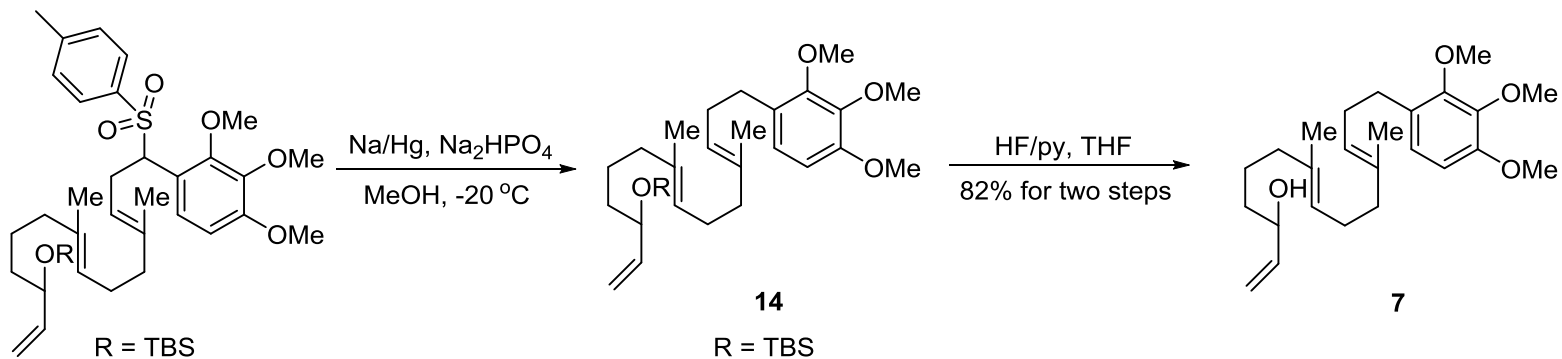
Dess-Martin Oxidation



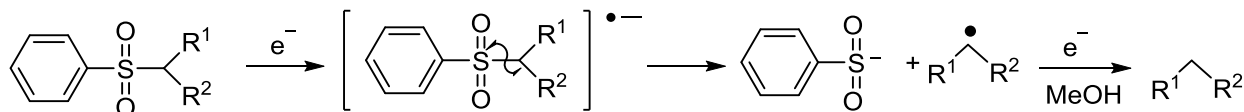
Total Synthesis of Mycoleptodiscin A

IV. Synthesis

Construction of polyene 7 – Part 3



Reductive desulfonylation



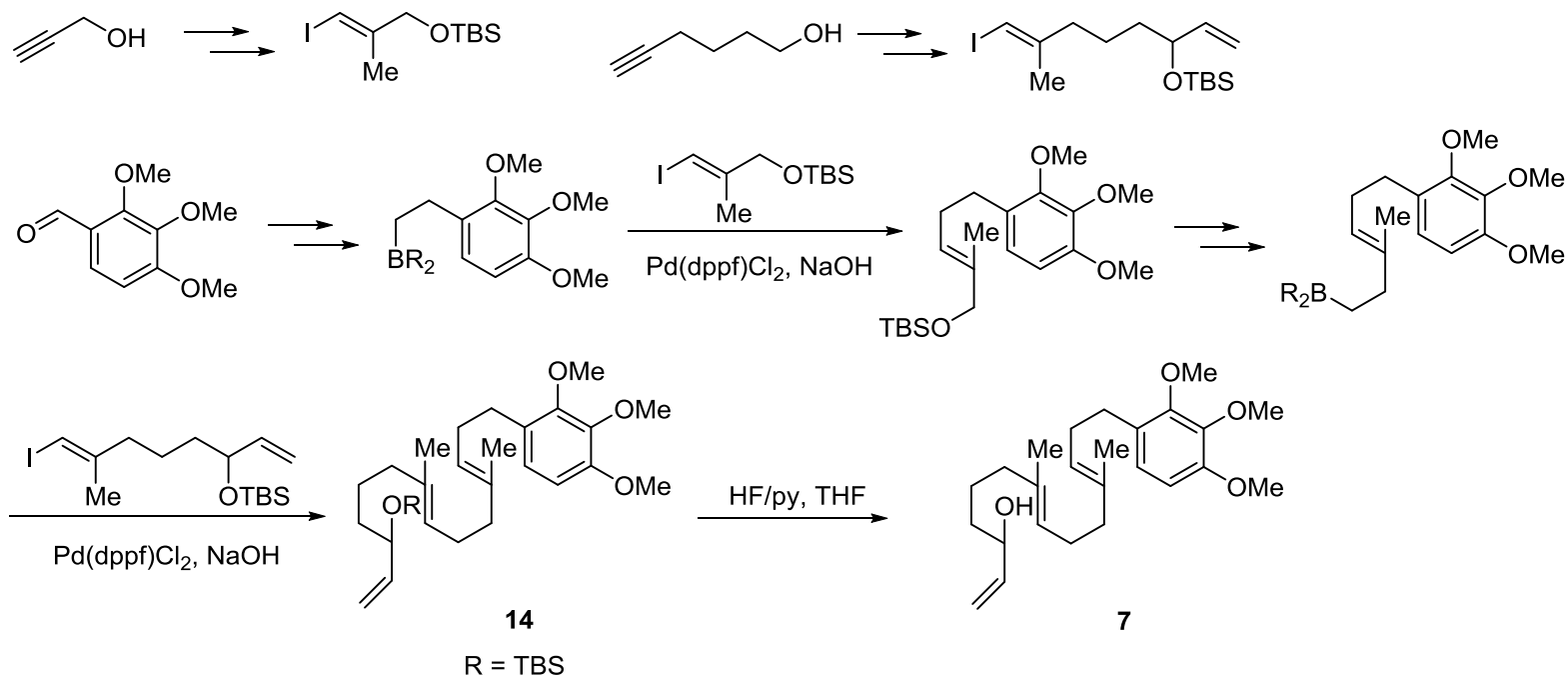
MeOH is essential to avoid beta-elimination (the Julia Reaction)

Similar single electron transfer (SET) reduction was also used at the last step to deprotect RNHTf by Mg/NH₄Cl/MeOH.

Total Synthesis of Mycoleptodiscin A

IV. Synthesis

Comparison with another route using Suzuki-Miyaura coupling as key step (in SI)



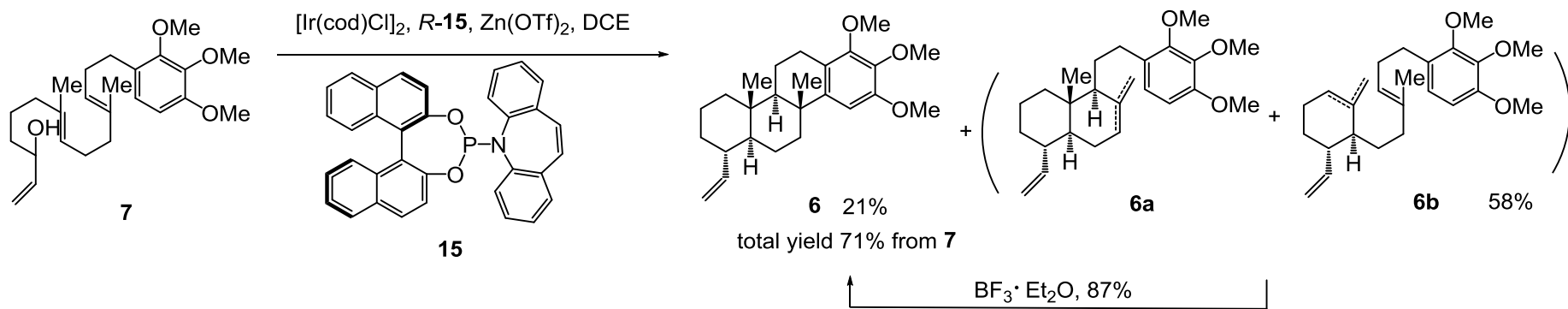
Suzuki-Miyaura route: longest linear sequence is 9 steps; number of overall steps is 15 steps; overall yield is 17 %; a few intermediates are volatile.

Sulfone alkylation route: longest linear sequence is 11 steps; number of overall steps is 13 steps; overall yield is 24 %; no volatile intermediates; more efficient and reliable on large scale.

Total Synthesis of Mycoleptodiscin A

IV. Synthesis

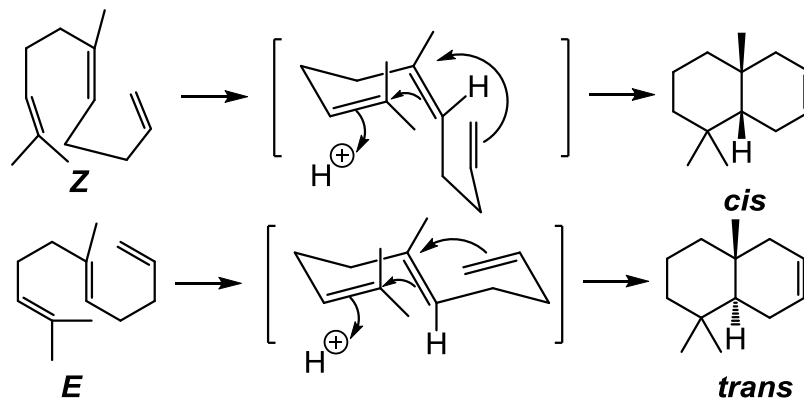
Construction of the tetracycle framework



Note: Olefin **6**, **6a** and **6b** have same polarities and cannot be separated with silica gel column, preparative TLC or HPLC. Their structures are postulated based on the NMR and mass spectroscopy of the mixture.

Biomimetic Polyene Cyclizations: catalytic enantioselective cyclizations (brønsted/Lewis acid catalyst, organo-catalyst and transition-metal catalyst).

Stork-Eschenmoser biogenic isoprene rule: polyene cyclization could be rationalized on stereoelectronic considerations; reaction is in defined conformations and product has predicted stereochemistry from starting materials.



G. Stork, A.W. Burgstrahler, *J. Am. Chem. Soc.* **1955**, *77*, 5068.

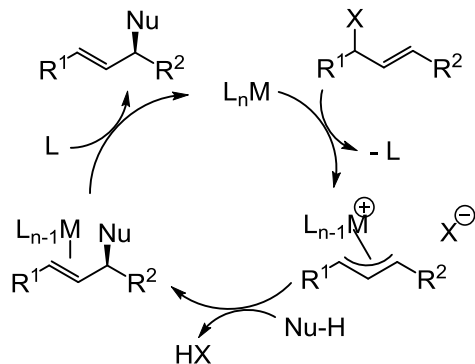
A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta.* **1955**, *38*, 1890.

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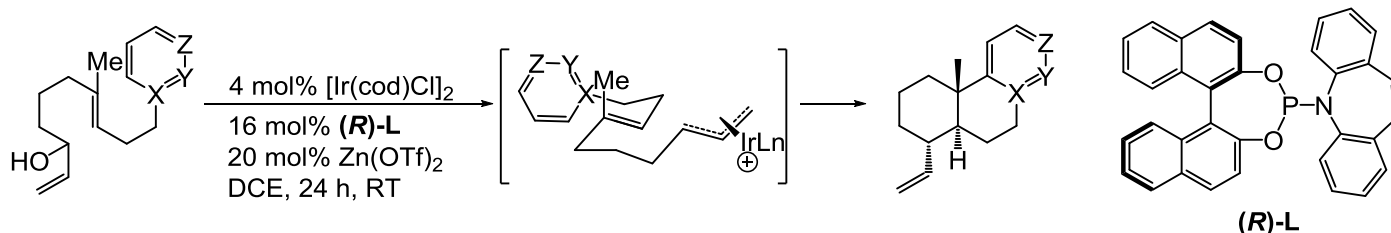
IV. Synthesis

Construction of the tetracycle framework

Iridium-Catalyzed allylic substitution: *O*-, *N*-, and *C*- nucleophiles were introduced enantioselectively at the branched position; cyclometalation is the key step to form active catalyst species; high enantioselectivity depends on selective oxidative addition step.



Carreira cyclization: *Iridium-Catalyzed enantioselective polyene cascade cyclization from unactivated, branched racemic allylic alcohols; the catalyst only has a direct stereocontrol effect over the first cyclization event; the closure of the subsequent ring is stereoselectively encoded by the first ring according to Stork–Eschenmoser paradigm.*



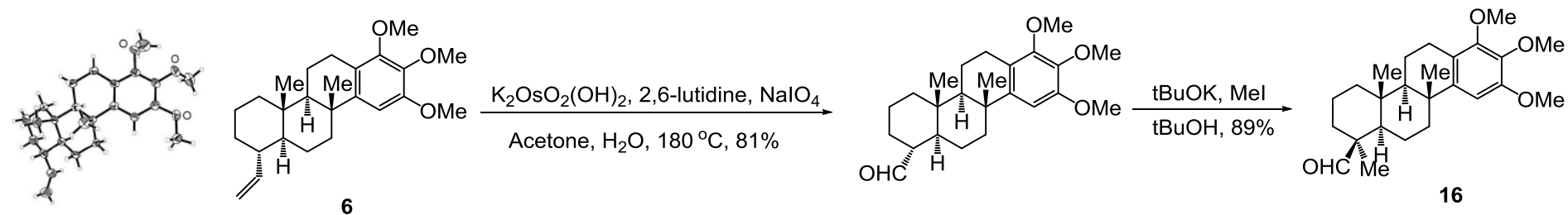
L. M. Stanley, J. F. Hartwig, *Acc. Chem. Res.* **2010**, 43, 1461.

J. F. Hartwig, M.J. Pouy, *Top. Organomet. Chem.* P.G. Andersson, Ed.; Springer-Verlag: Berlin, Germany, **2011**, 34, 169-208.

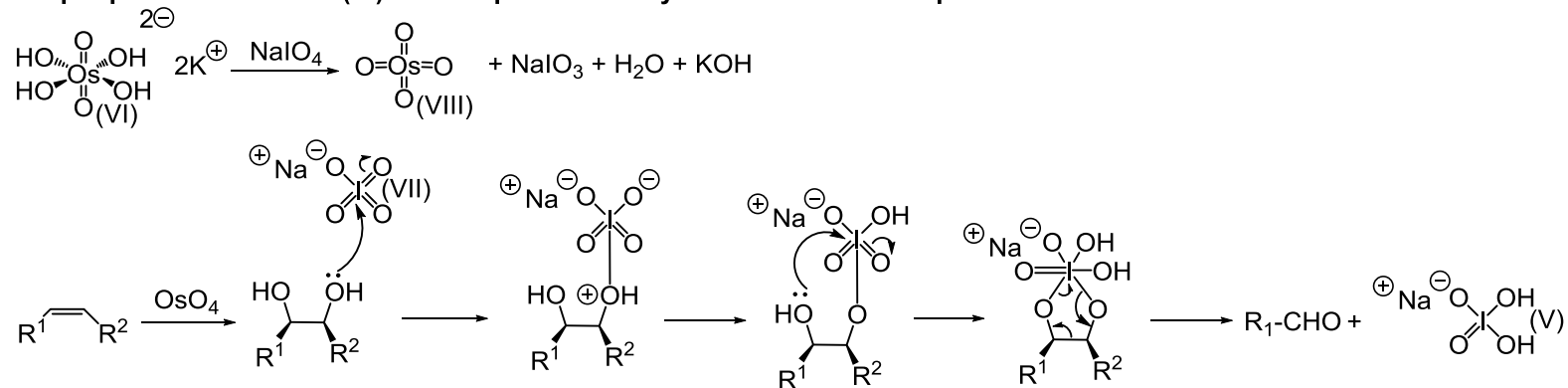
M. A. Schafrath, D. Sarlah, S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2012**, 134, 20276.

Total Synthesis of Mycoleptodiscin A

IV. Synthesis

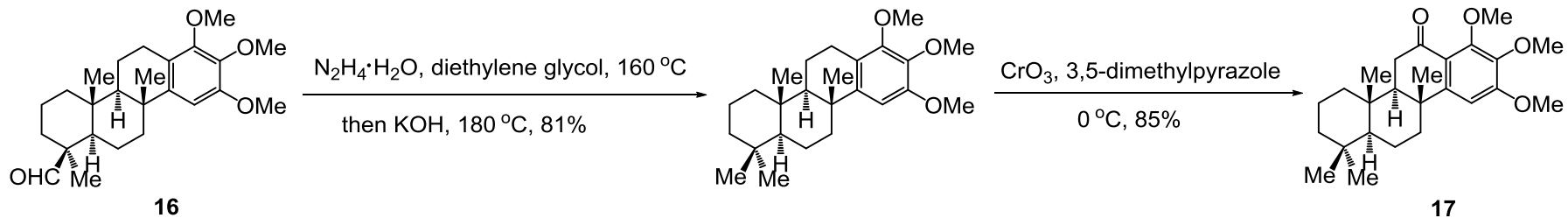


One-pot potassium osmate(VI)/sodium periodate dihydrate then oxidation process

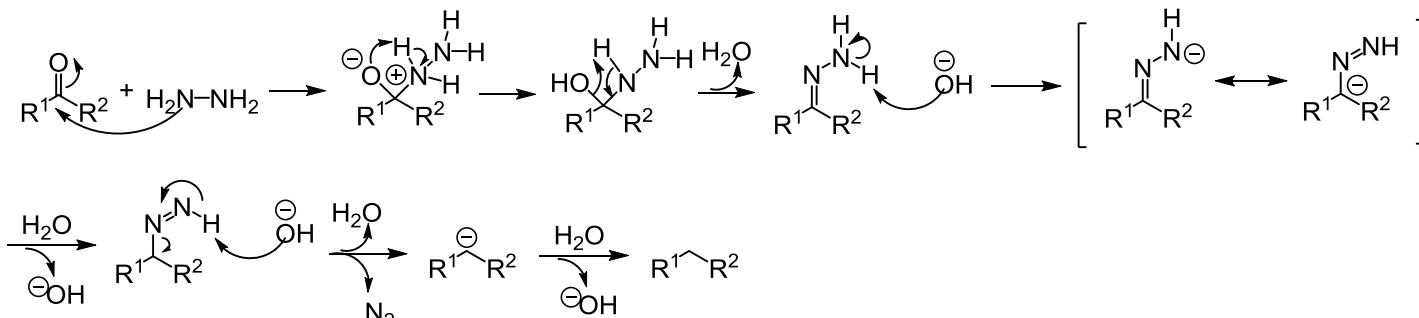


Total Synthesis of Mycoleptodiscin A

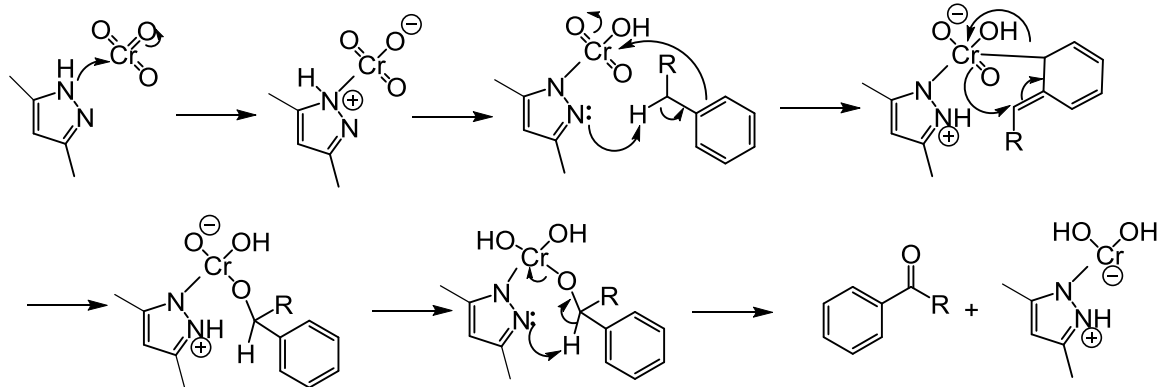
IV. Synthesis



Wolff-Kishner Reduction (Huang-Minlon Modification)

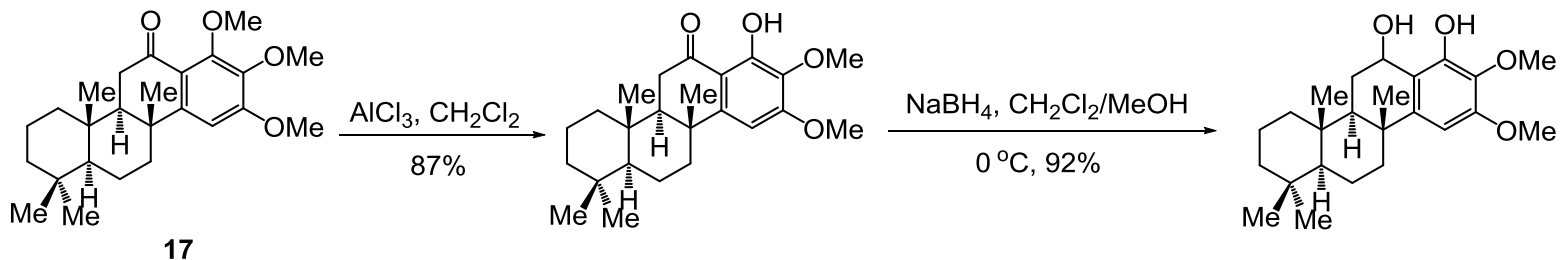


Benzylic oxidation by 3,5-dimethylpyrazole chromium trioxide complex

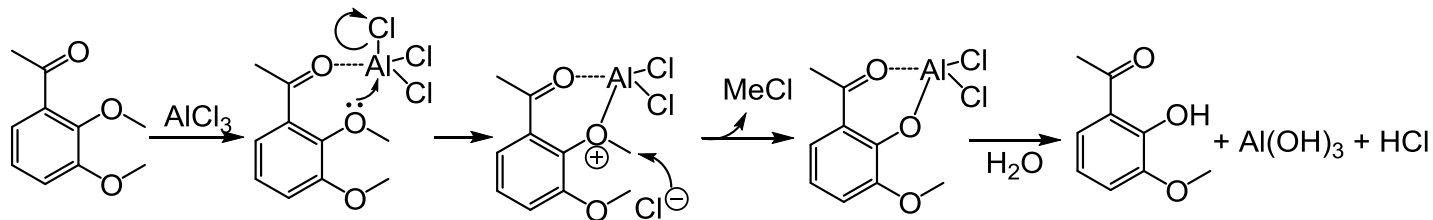


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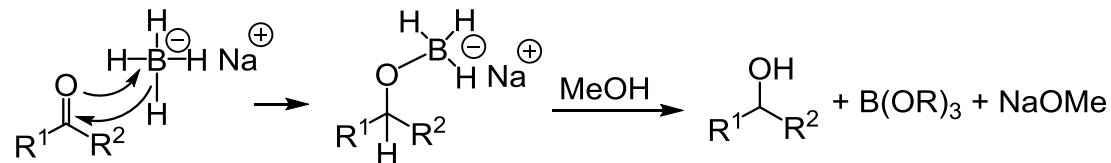
IV. Synthesis



AlCl_3 demethylation



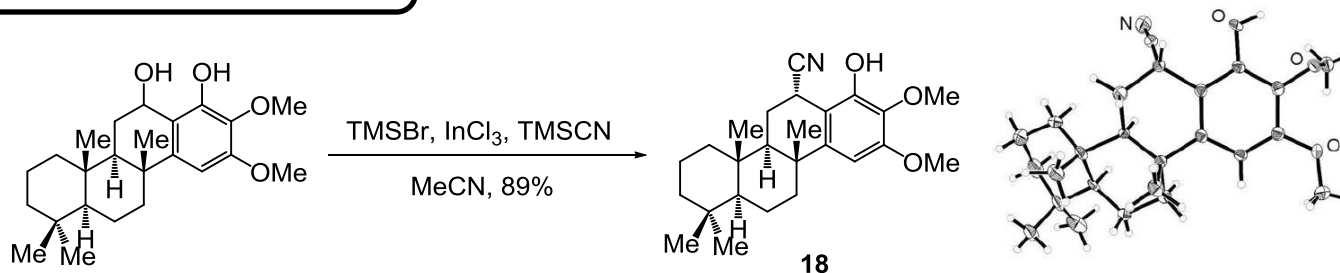
NaBH_4 reduction



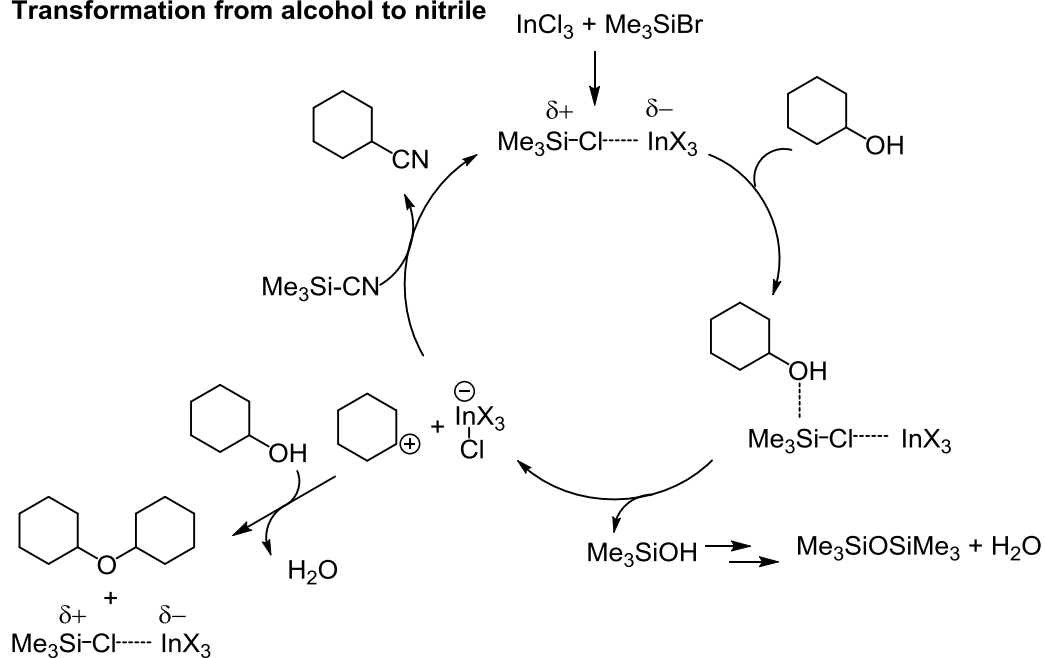
Total Synthesis of Mycoleptodiscin A

IV. Synthesis

Benzylic cyanation: $\text{TMSBr}/\text{InCl}_3/\text{TMSCN}/\text{MeCN}$ was the optimized condition

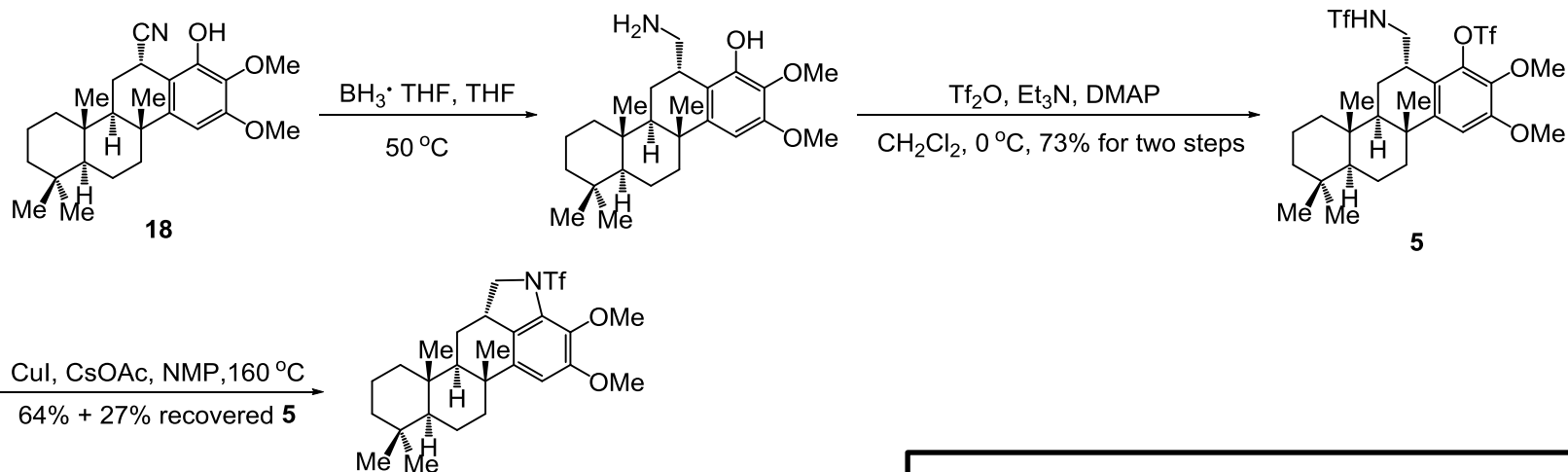


Transformation from alcohol to nitrile



Total Synthesis of Mycoleptodiscin A

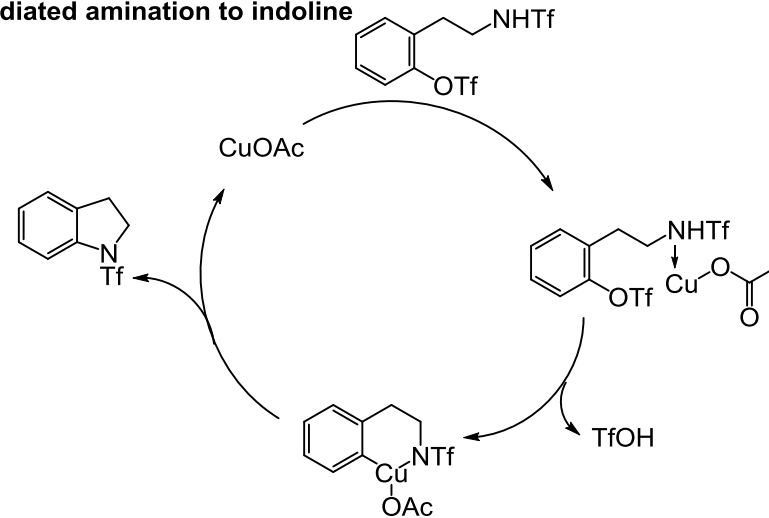
IV. Synthesis



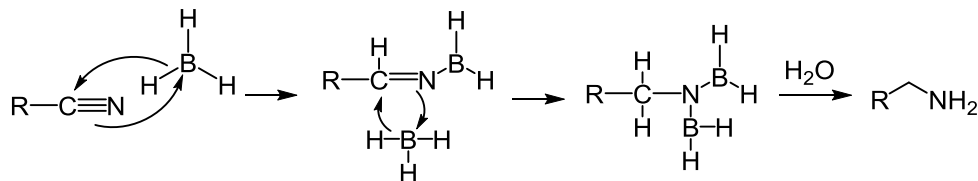
Screening of indoline cyclization:

Buchwald–Hartwig amination: Failed in various Pd/L combinations, which only resulted the free phenol;
Modified Fukuyama condition: $\text{CuI}/\text{CsOAc}/\text{NMP}$. NMP gave much better yield than previously reported DMSO.

Cu-mediated amination to indoline



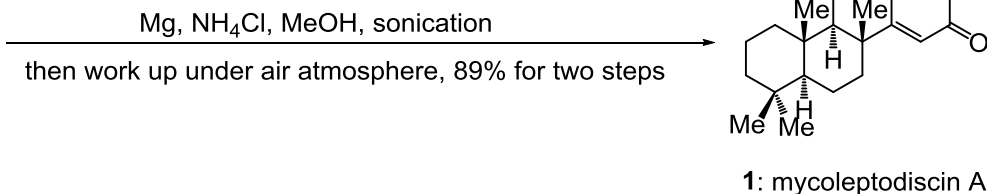
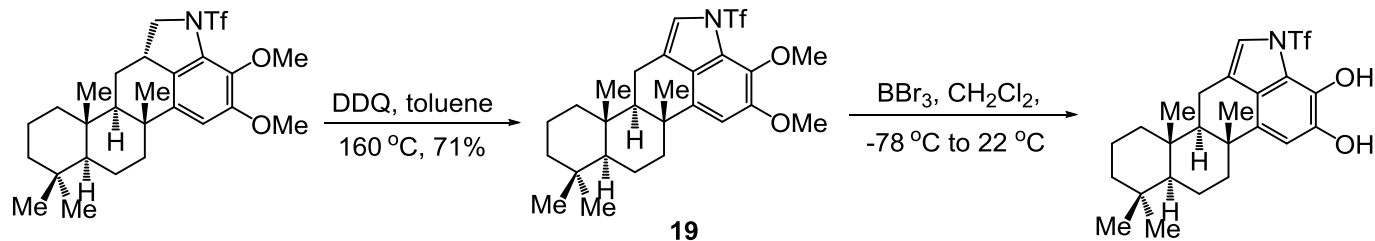
Nitrile reduction



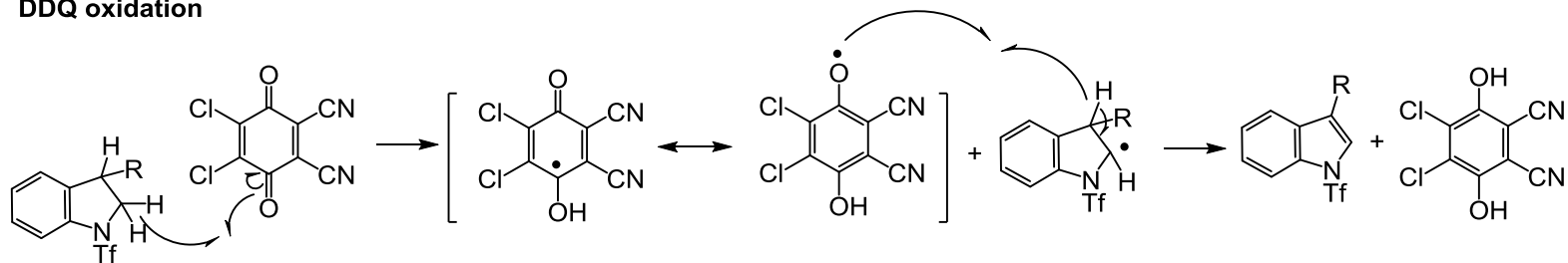
Total Synthesis of Mycoleptodiscin A

IV. Synthesis

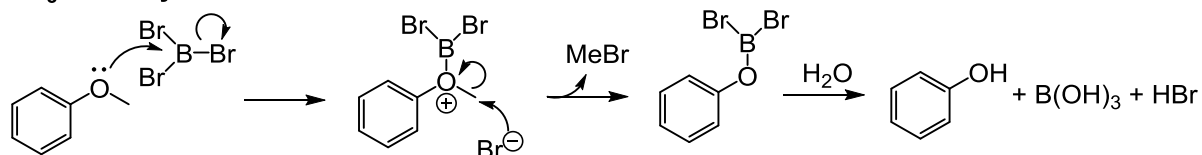
End of the game



DDQ oxidation



BBr₃ demethylation



V. Summary

- The first total synthesis of mycoleptodiscin A, a structurally unusual indolosesquiterpenoid possessing an ortho-benzoquinone motif, has been accomplished in 26 steps.

The key features:

- Aryl triene intermediate was synthesized through sulfone alkylation of two readily available fragments.
- The tetracyclic core of the molecule was assembled through a scalable highly enantioselective iridium-catalyzed polyene cyclization.
- The benzylic homologation was achieved by a cationic cyanation.
- The multisubstituted indole ring was constructed via a Cu-mediated intramolecular C-N bond formation at a late stage.