Literature Report 2

Total Synthesis of Caribenol A and Caribenol B

Reporter: Xiao-Yong Zhai
Checker: Shubo Hu
Date: 2017-04-24

Hao, H.-D.; Trauner, D.
J. Am. Chem. Soc. **2017**, *139*, 4117.

CV of Dirk Trauner

Dirk Trauner

Education:

- **1986–1991** B.S., University of Vienna
- **1992–1995** M.S., Free University of Berlin
- **1996–1997** Ph.D., University of Vienna
- **1998–2000** Postdoc., Memorial Sloan Kettering Cancer Center
- **2001–2008** Associate Professor, University of California, Berkeley
- **2009-2017** Professor, University of Munich and New York University

Research:

➢ chemical synthesis, natural product chemistry, neuroscience, cell biology and photopharmacology.

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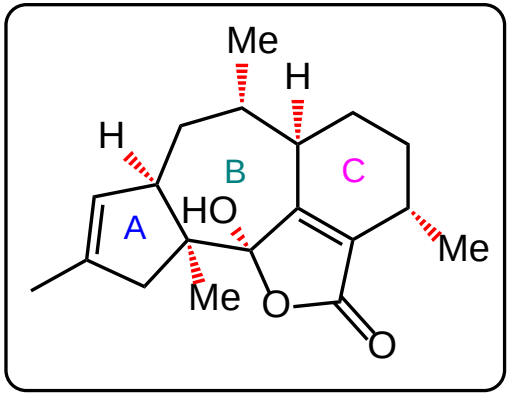
Introduction



Caribenol A

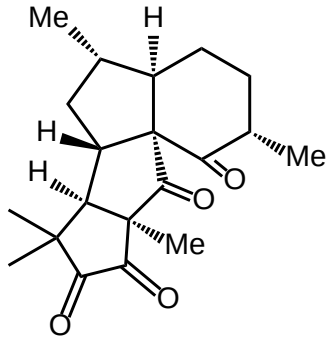
Pseudopterogorgia

- Isolated from the *Pseudopterogorgia elisabethae* in 2007;
- Exhibiting biological activity against *Mycobacterium tuberculosis* H37Rv and plasmodium;
- A caged structure and tricarbocyclic ring system with six stereocenters.

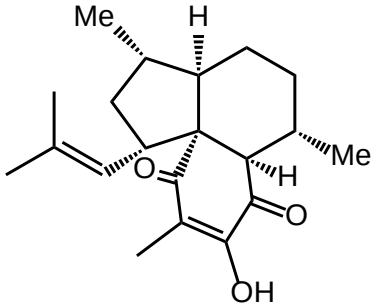
Wei, X.; Rodríguez, I. I.; Rodríguez, A. D.; Barnes, C. L. *J. Org. Chem*. **2007**, *72*, 7386.

Introduction

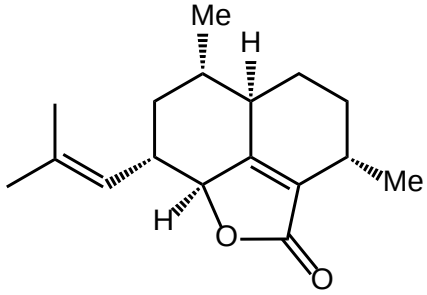
Natural products isolated from *Pseudopterogorgia elisabethae*



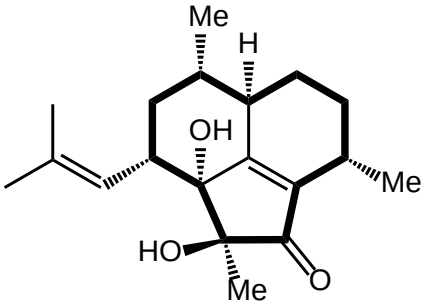
Aberrarone



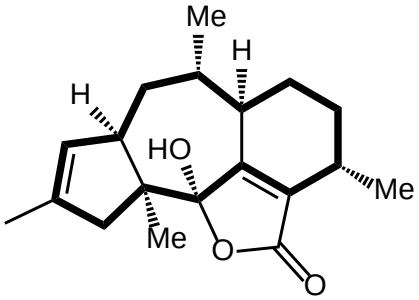
Elisabethin A



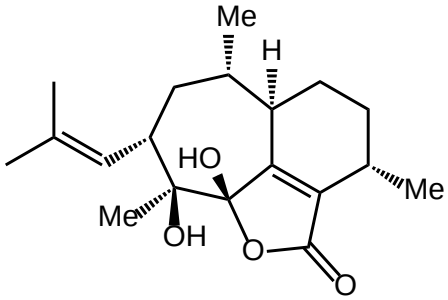
Amphilectolide



Caribenol B



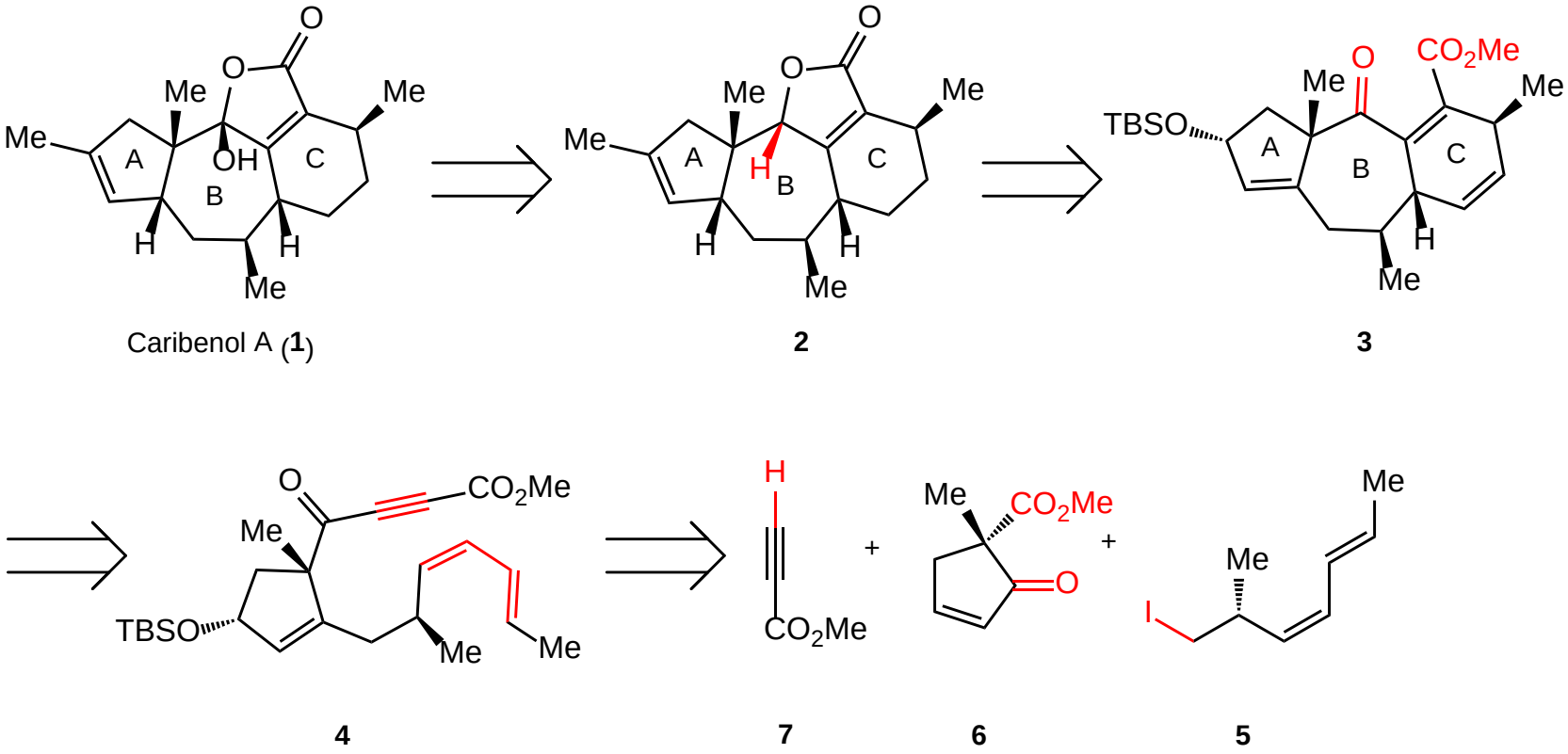
Caribenol A



Sandresolide B

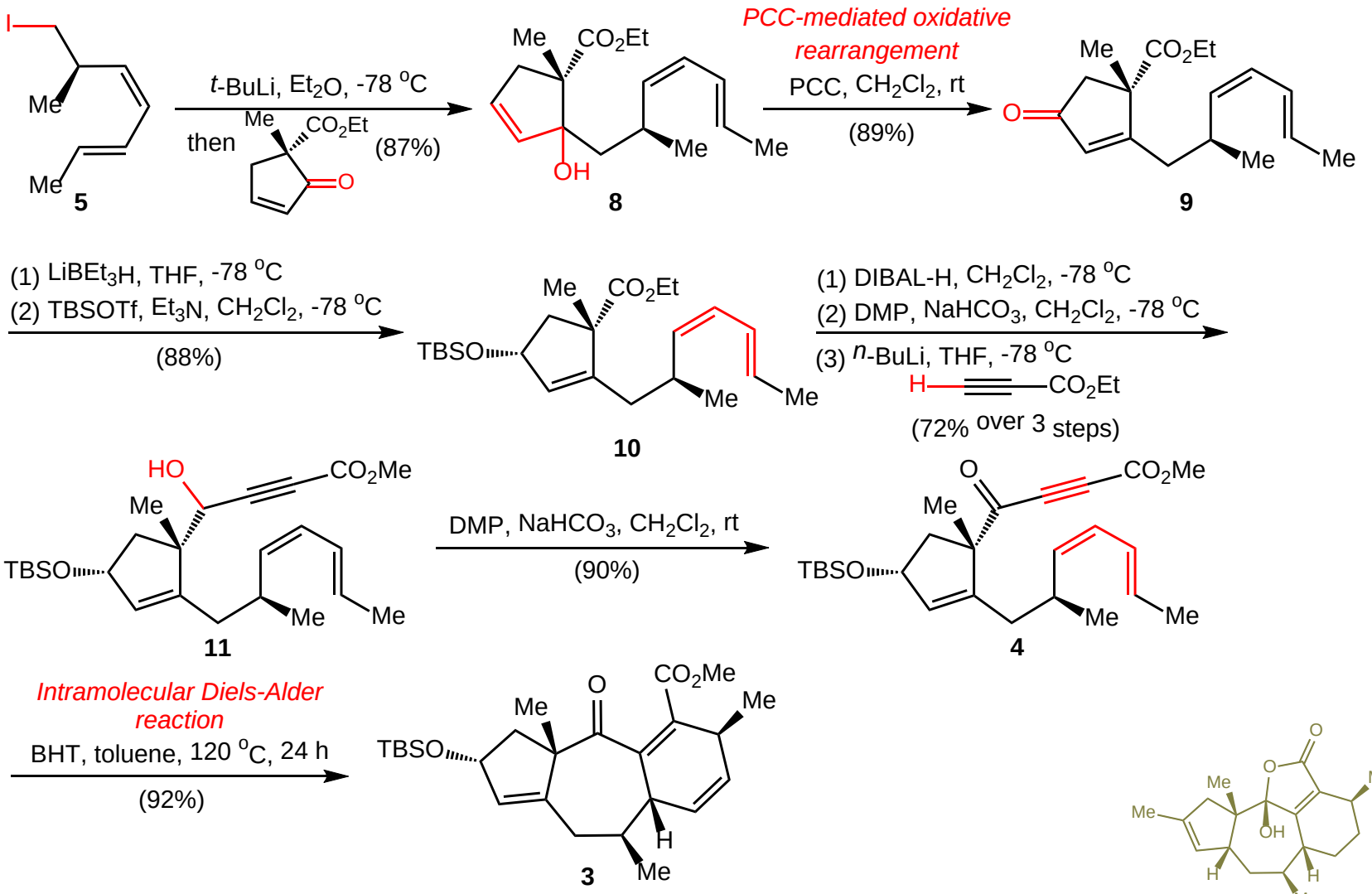
Wei, X.; Rodríguez, I. I.; Rodríguez, A. D.; Barnes, C. L. *J. Org. Chem*. **2007**, *72*, 7386.

Retrosynthetic analysis of Caribenol A

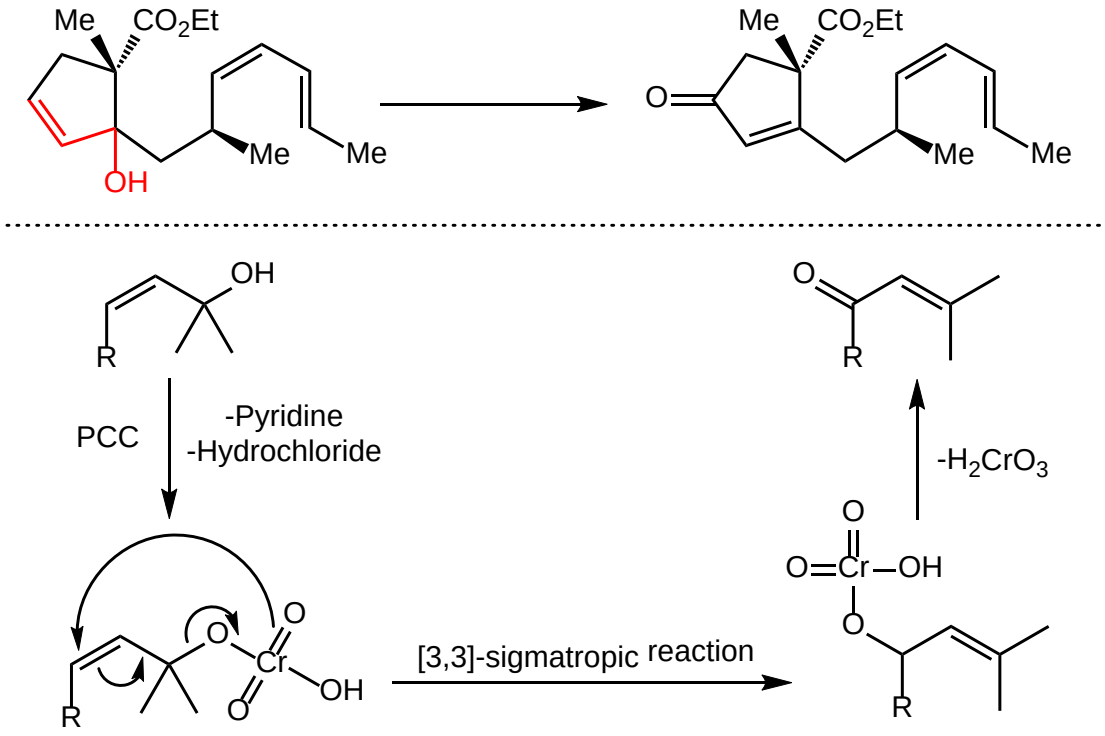


Liu, L-Z.; Han, J-C.; Yue, G-Z.; Li, C-C.; Yang, Z. *J. Am. Chem. Soc*. **2010**, *132*, 13608.

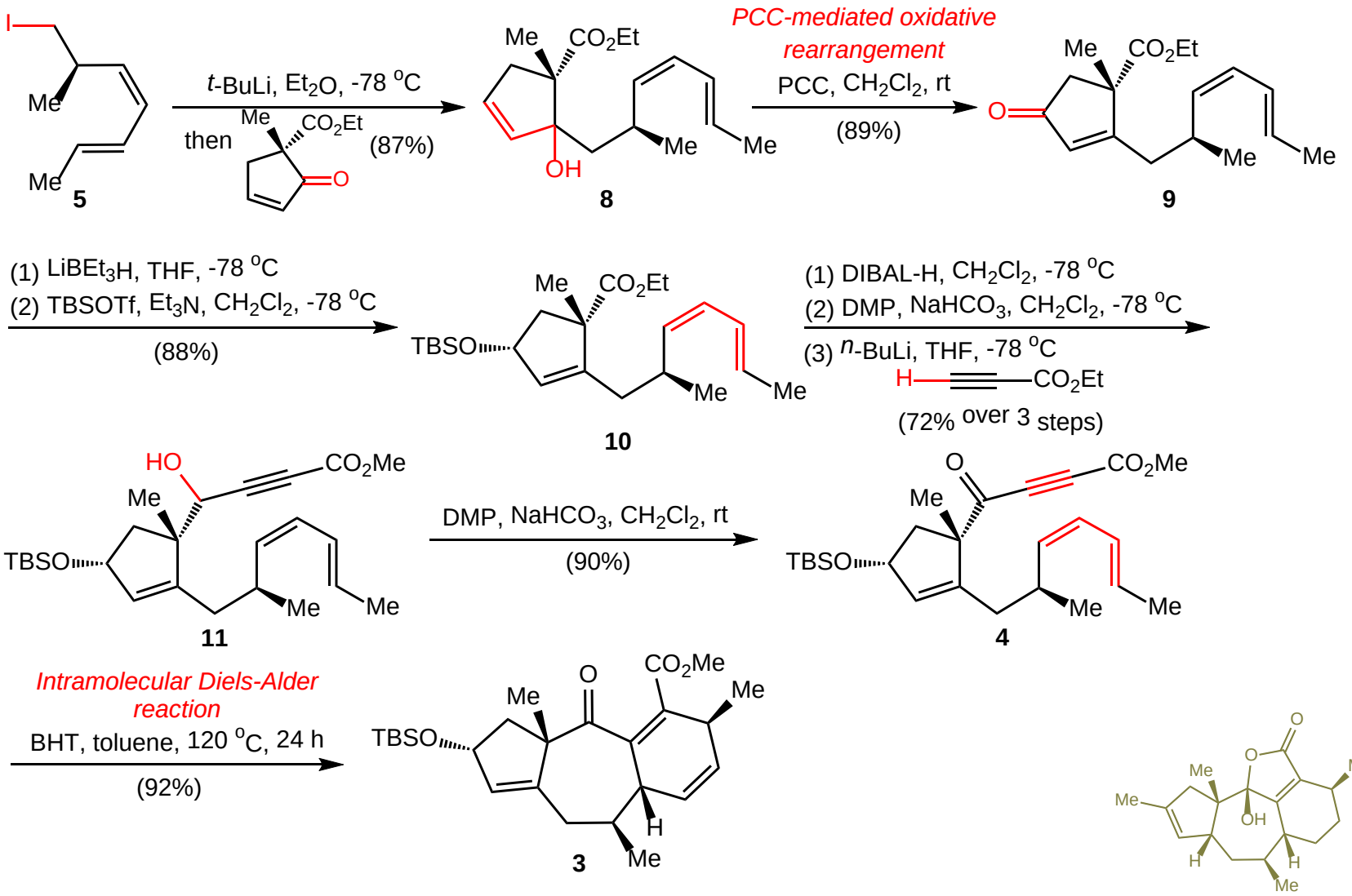
Total synthesis of Caribenol A



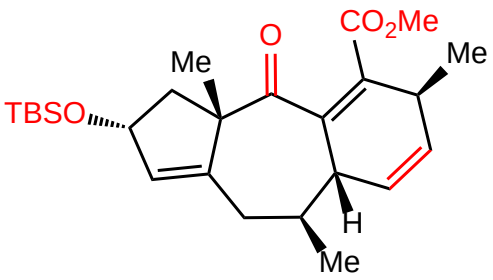
PCC mediated oxidative rearrangement



Total synthesis of Caribenol A



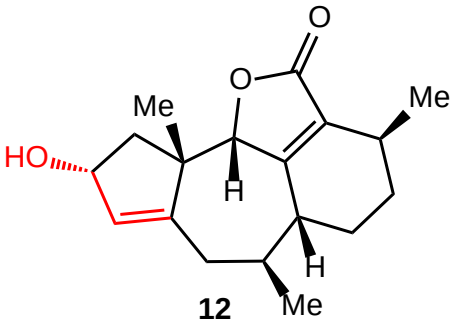
Total synthesis of Caribenol A



3

(1) $Rh(PPh_3)_3Cl$, H_2, PhH, 66 °C
(2) HF/Pry,THF, rt
(3) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, 0 °C

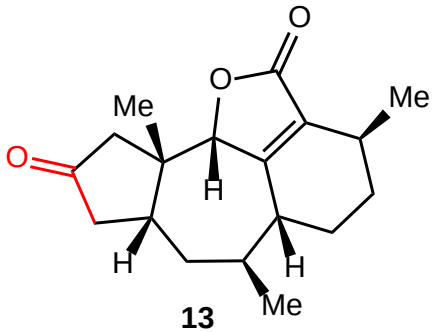
(80% over 3 steps)



12

(1) TPAP, NMO, 4 Å MS
CH_2Cl_2, rt
(2) Pd/C, H_2, THF

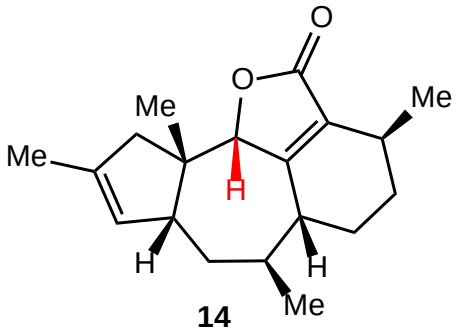
(86 % over 2 steps)



13

(1) KHMDS, THF
Comins reagent, -78 °C
(2) $Pd(PPh_3)_4$, Me_2Zn, THF, rt

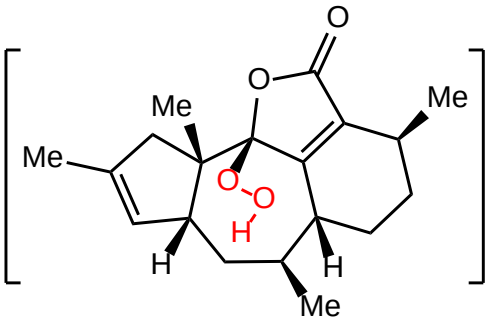
(77 % over 2 steps)



14

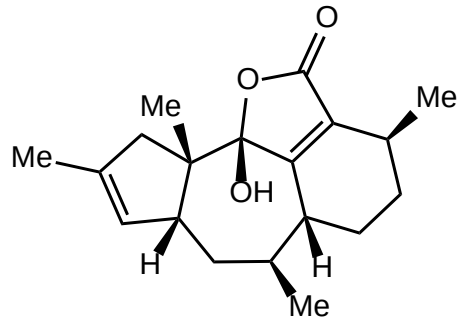
O_2, DMF, K_2CO_3
$P(OEt)_3$, 60 °C, 80 h

(66 %)



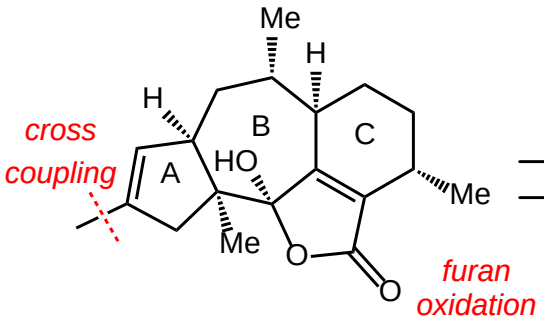
15

$P(OEt)_3$

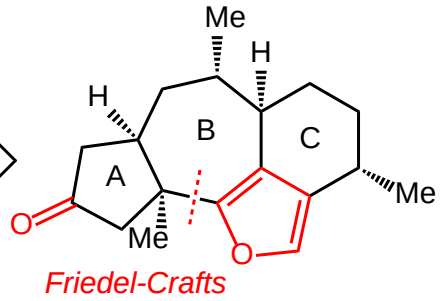


Caribenol A (**1**)

Retrosynthetic analysis of Caribenol A



Caribenol A (**1**)



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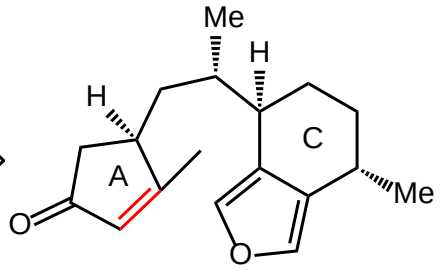

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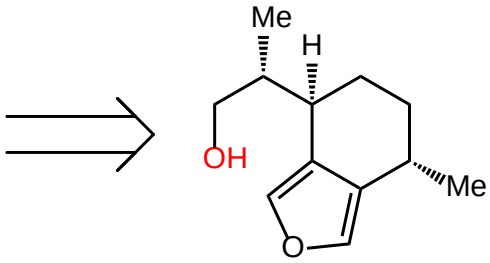
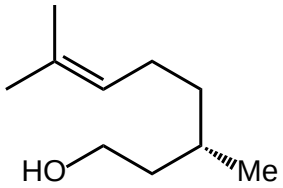


4

14 steps

gram scale



(-)-β-citronellol

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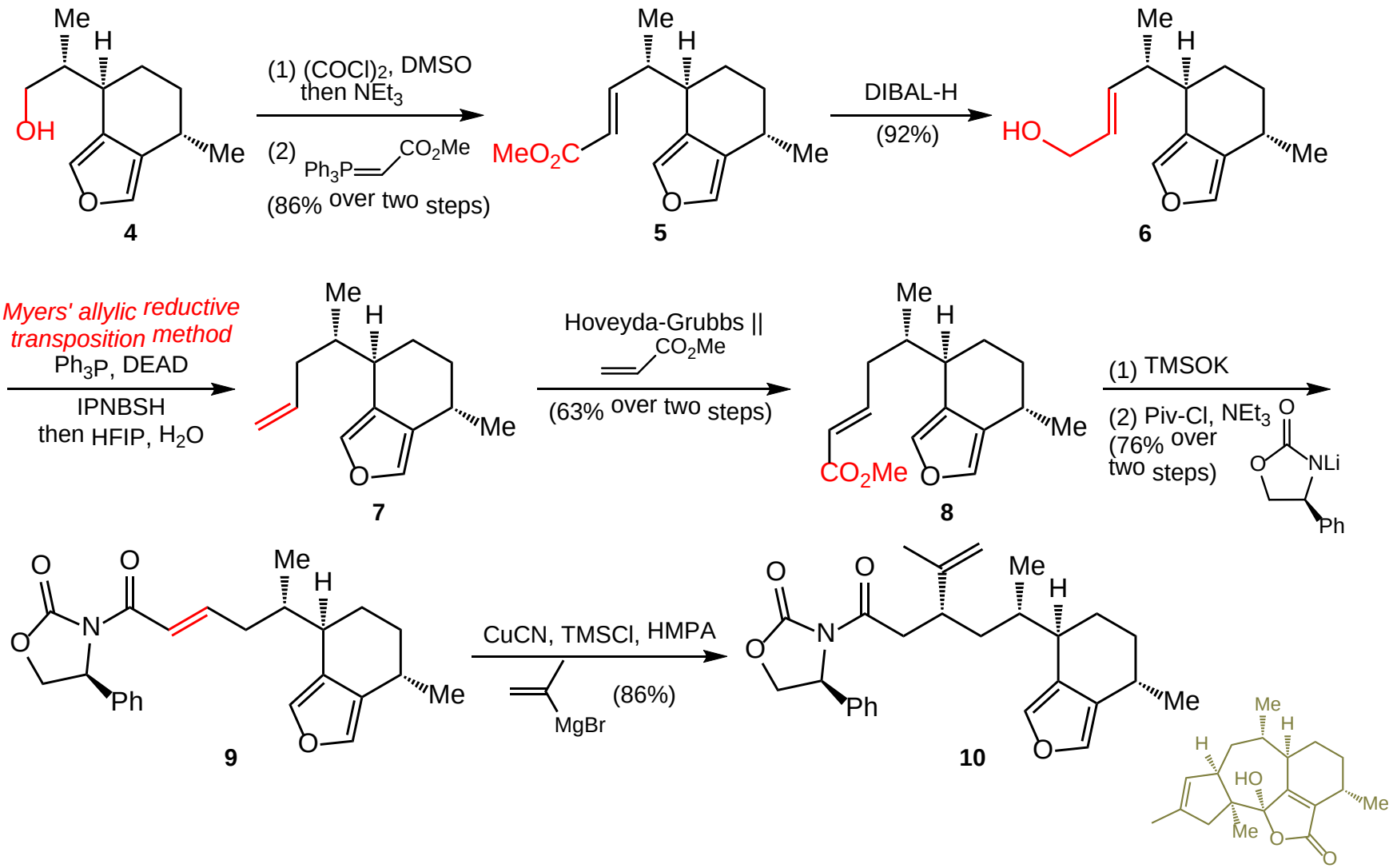
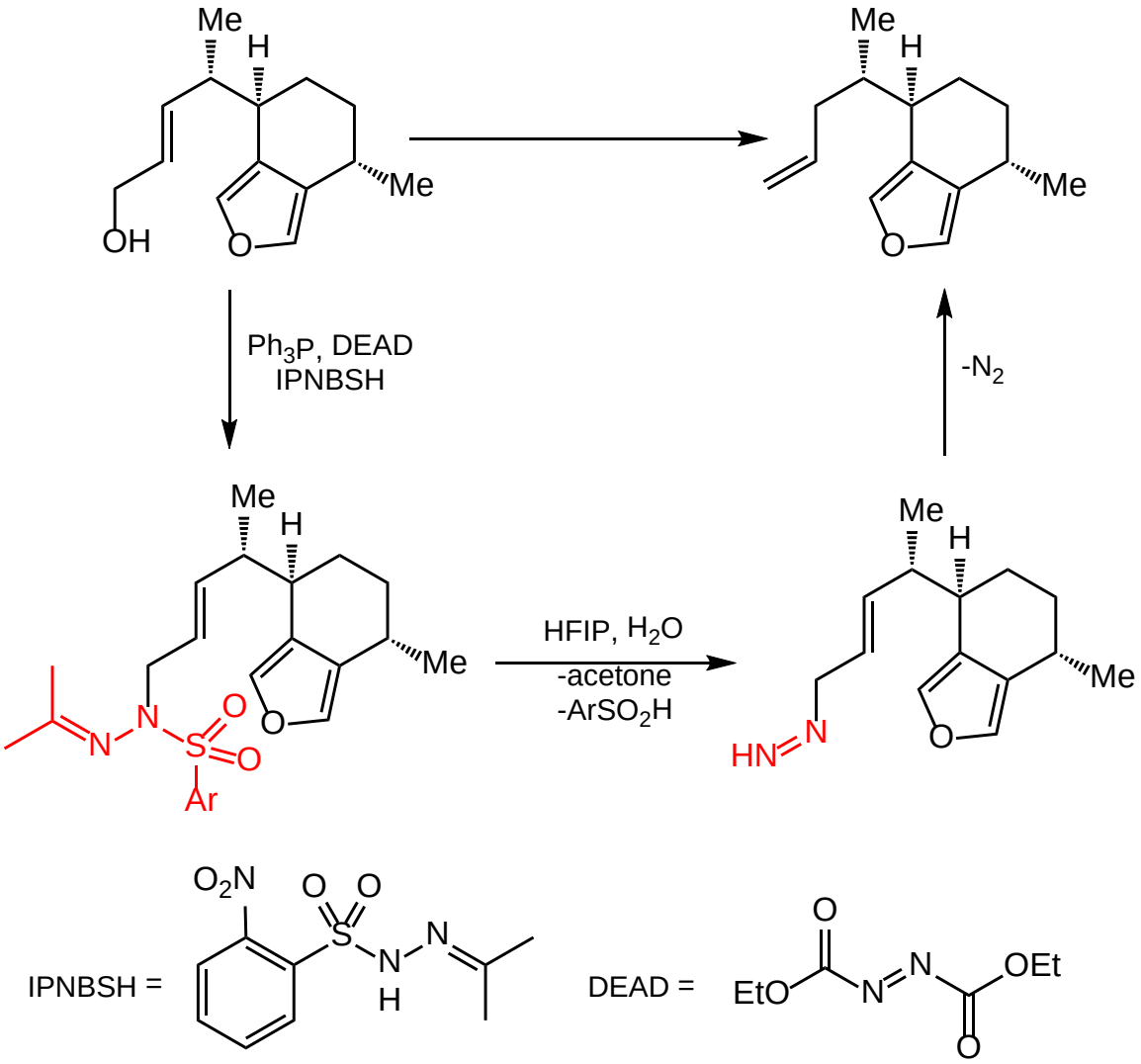
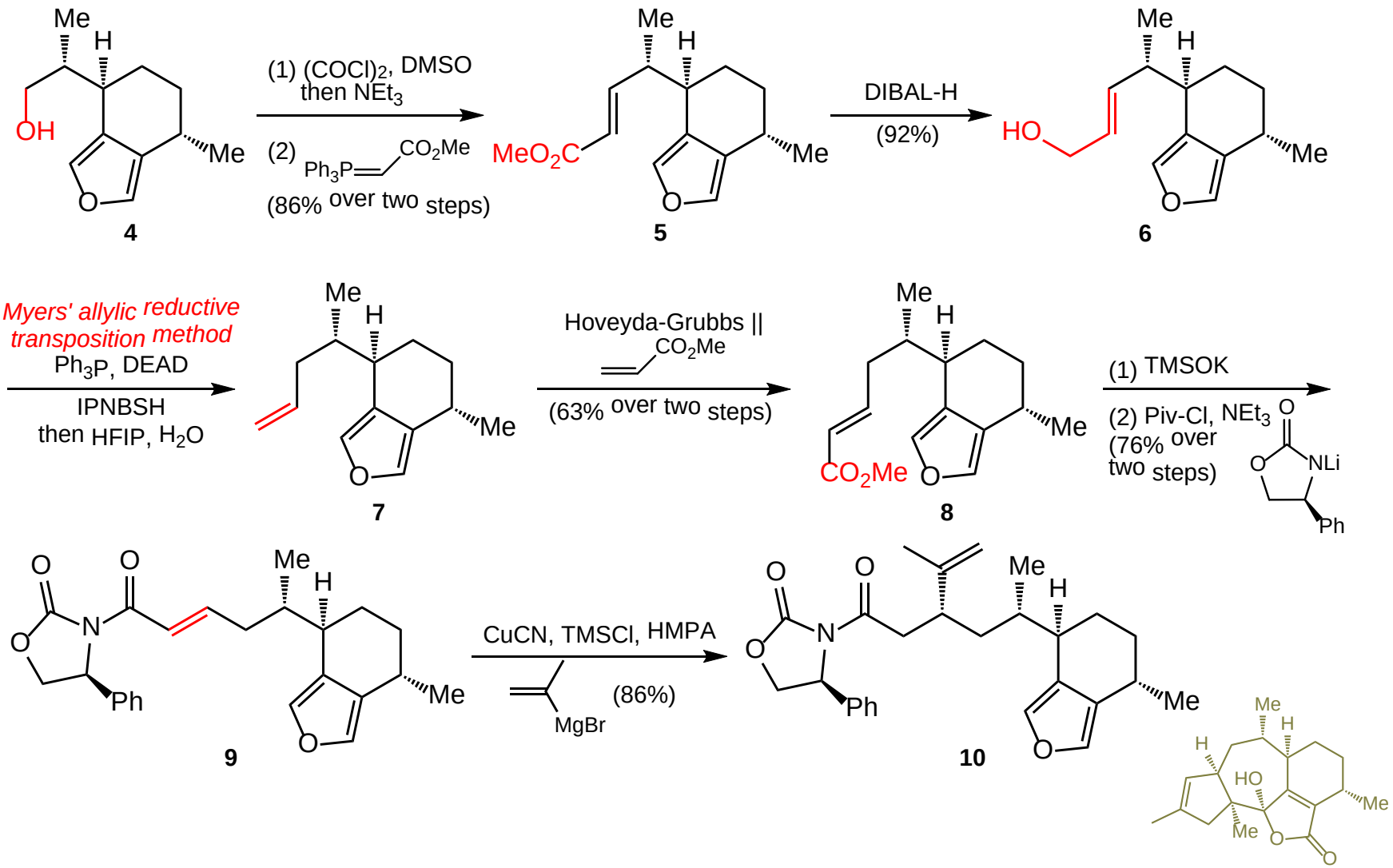
Total synthesis of Caribenol A



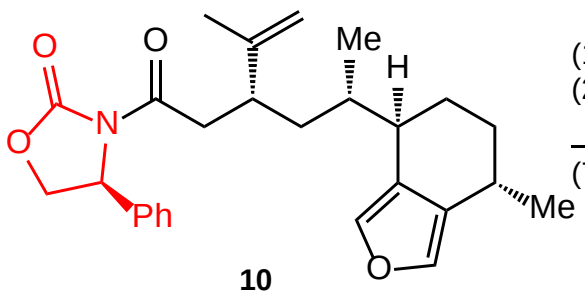
Myers' allylic reductive transposition method



Total synthesis of Caribenol A



Total synthesis of Caribenol A



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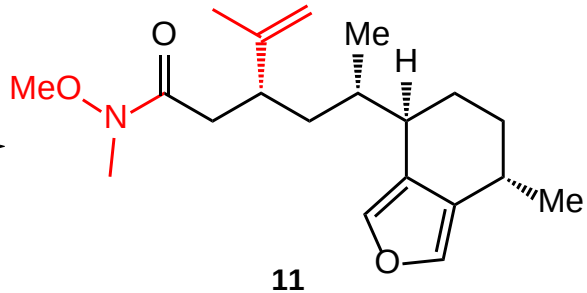
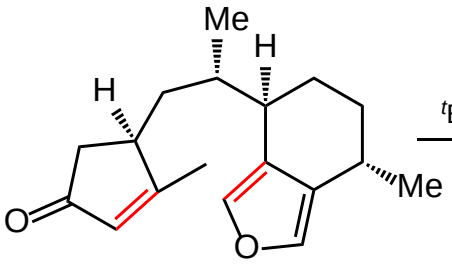
(1) $Sm(OTf)_3$, MeOH
(2) HNMe(OMe)•HCl
Me_2AlCl

(76% over two steps)



11

(1)  MgBr (94 %)
(2) H-G || (77 %)



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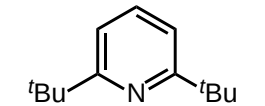
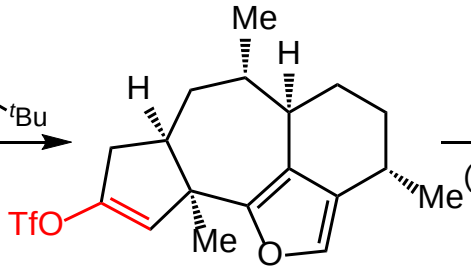


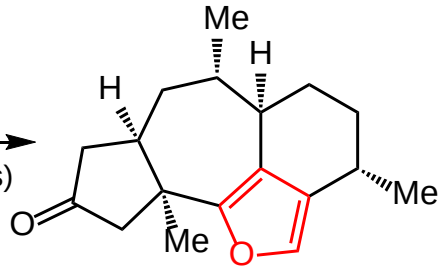
Tf_2O



12

TMSOK

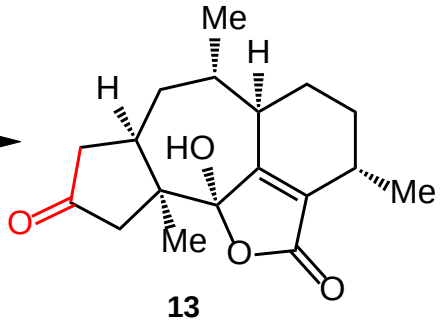
(53 % over two steps)



2

CH_3CO_3H
NaOAc

(72 %)

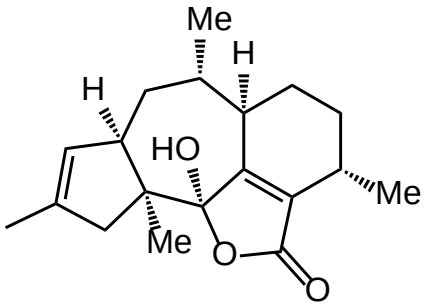


13

Barton's protocol for vinyl iodide formation

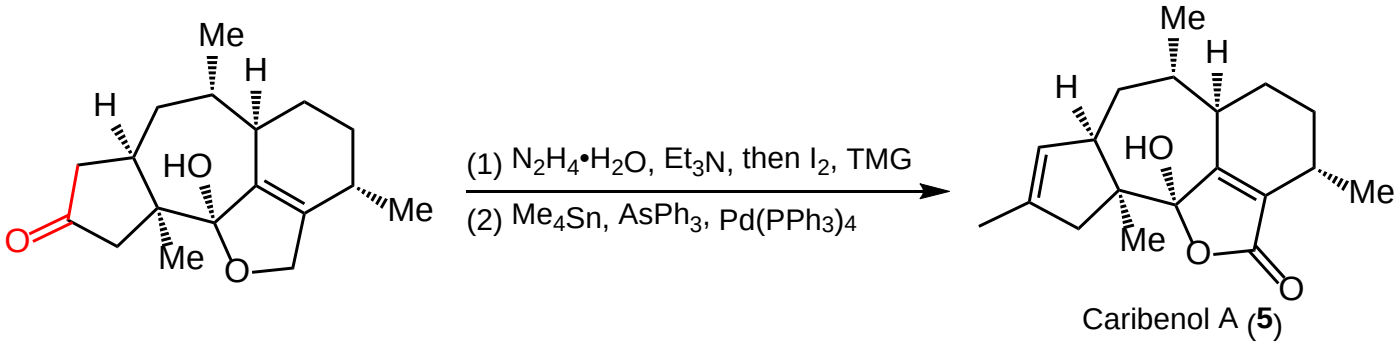
(1) N_2H_4•H_2O, Et_3N
then I_2, TMG (56 %)

(2) Me_4Sn, $AsPh_3$
$Pd(PPh_3)_4$ (33 %)

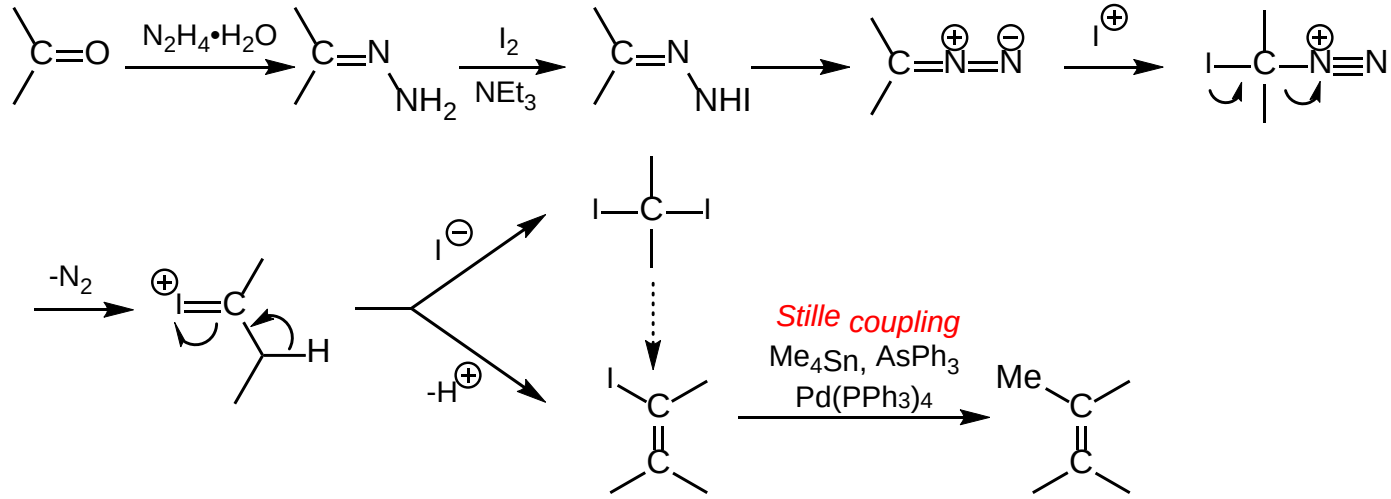


Caribenol A (**1**)

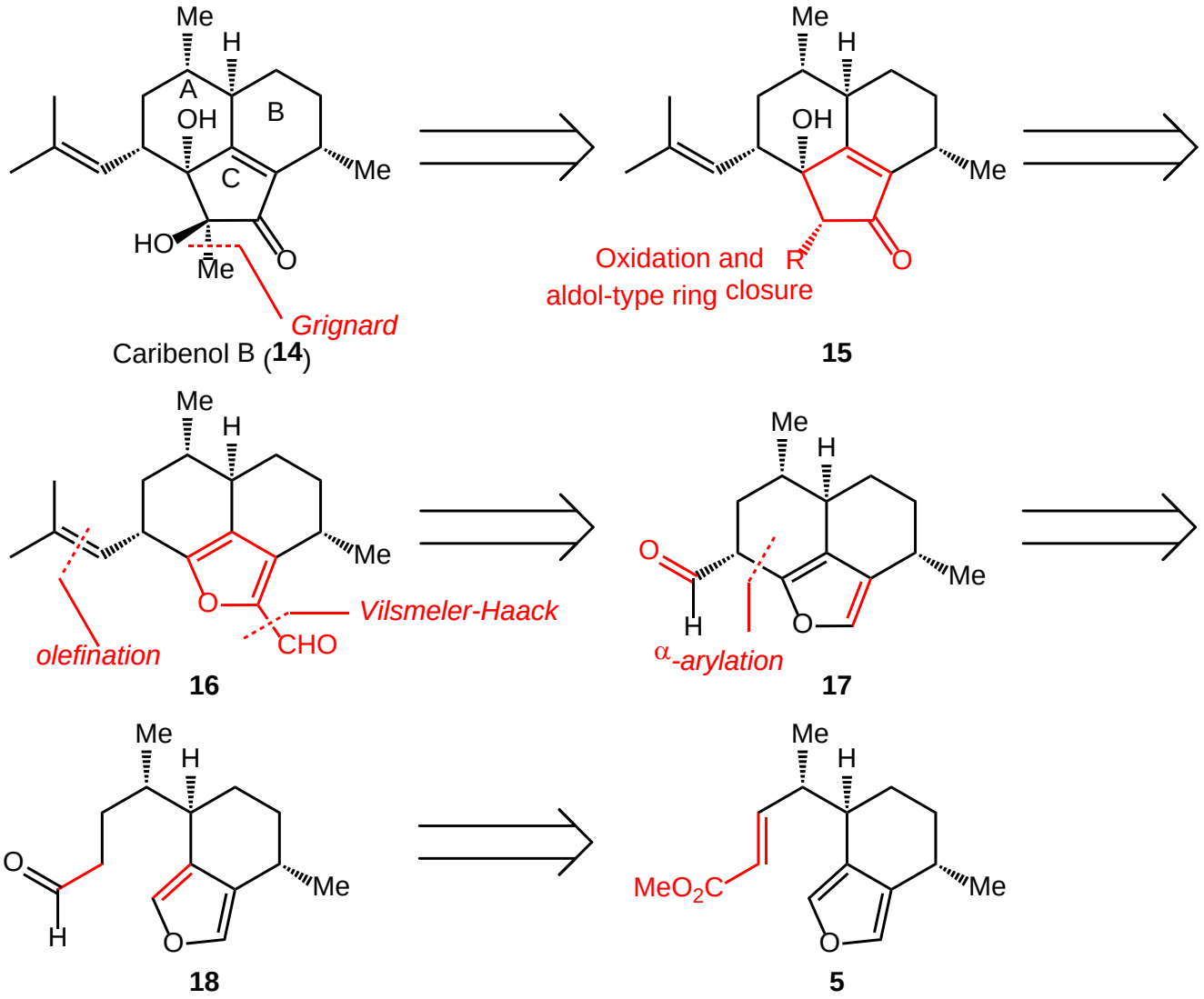
Barton's protocol for vinyl iodide formation



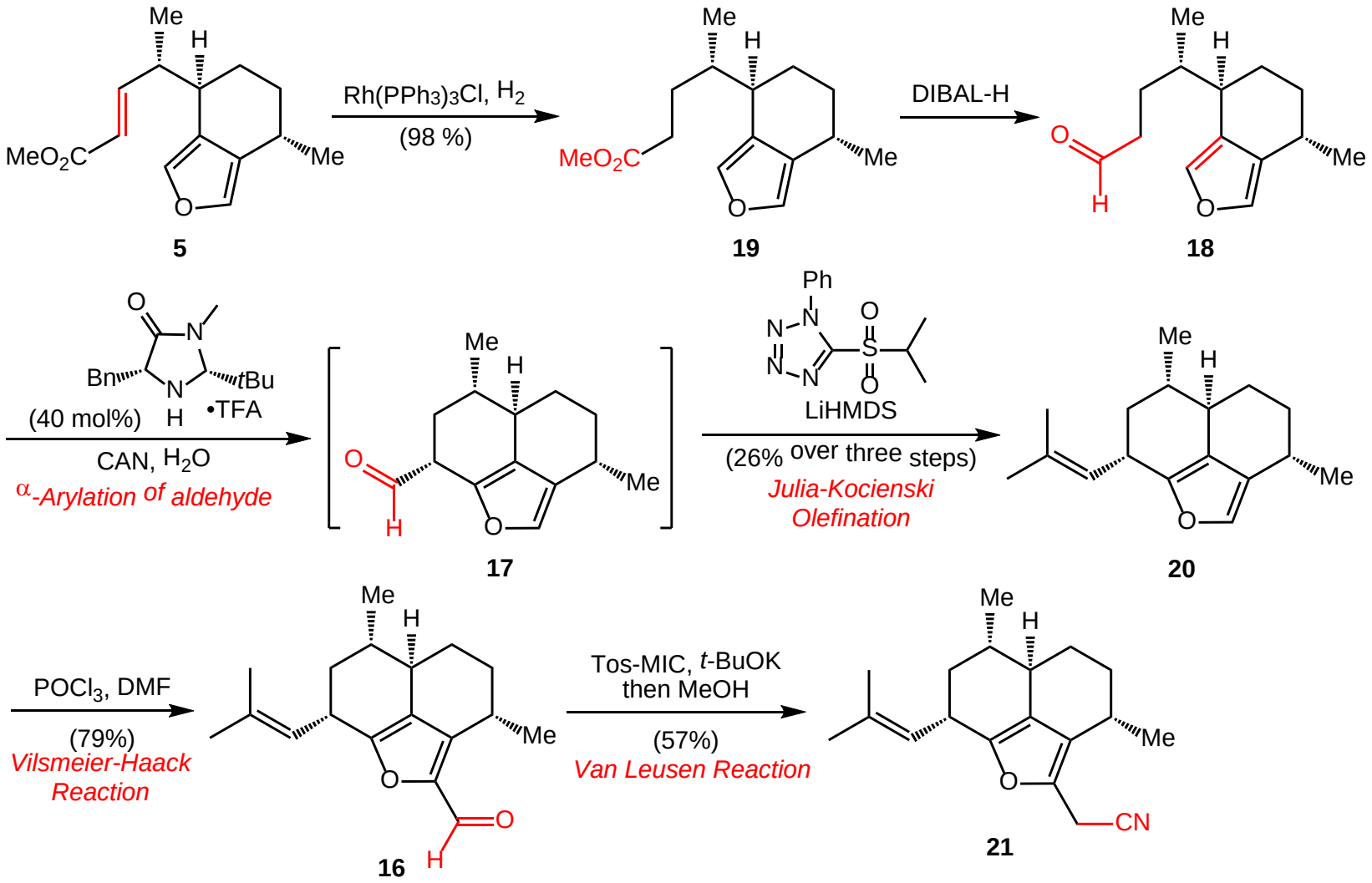
Caribenol A (**5**)



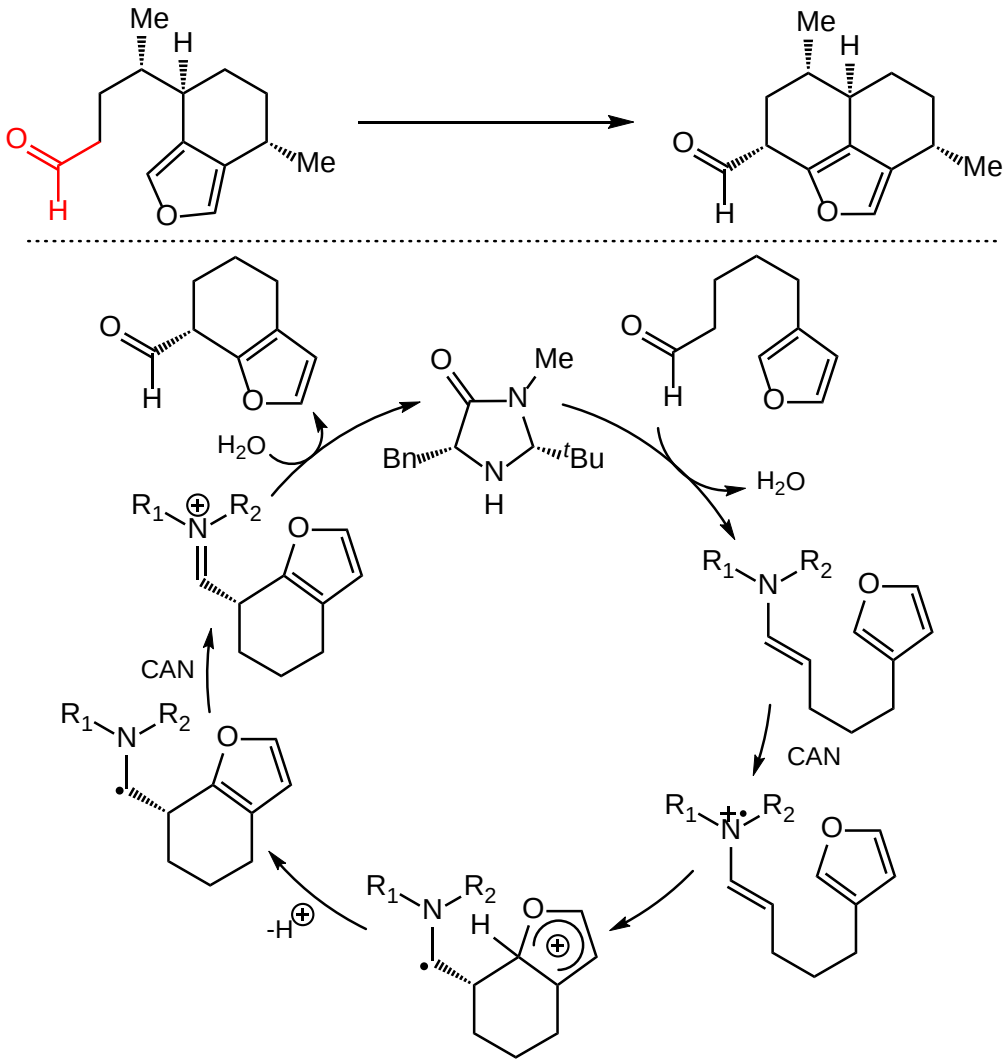
Retrosynthetic analysis of Caribenol B



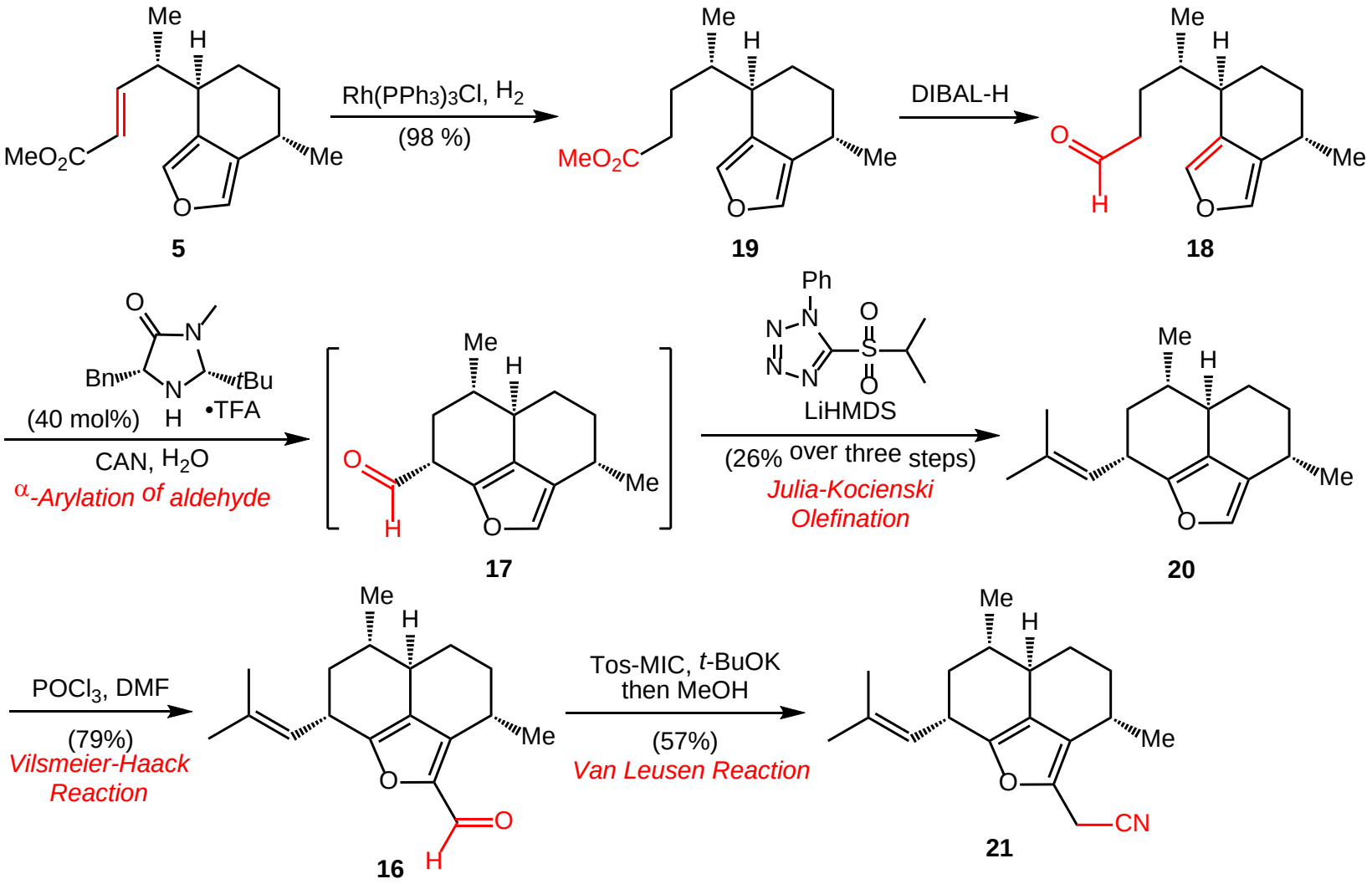
Total synthesis of Caribenol B



α-Arylation of aldehyde

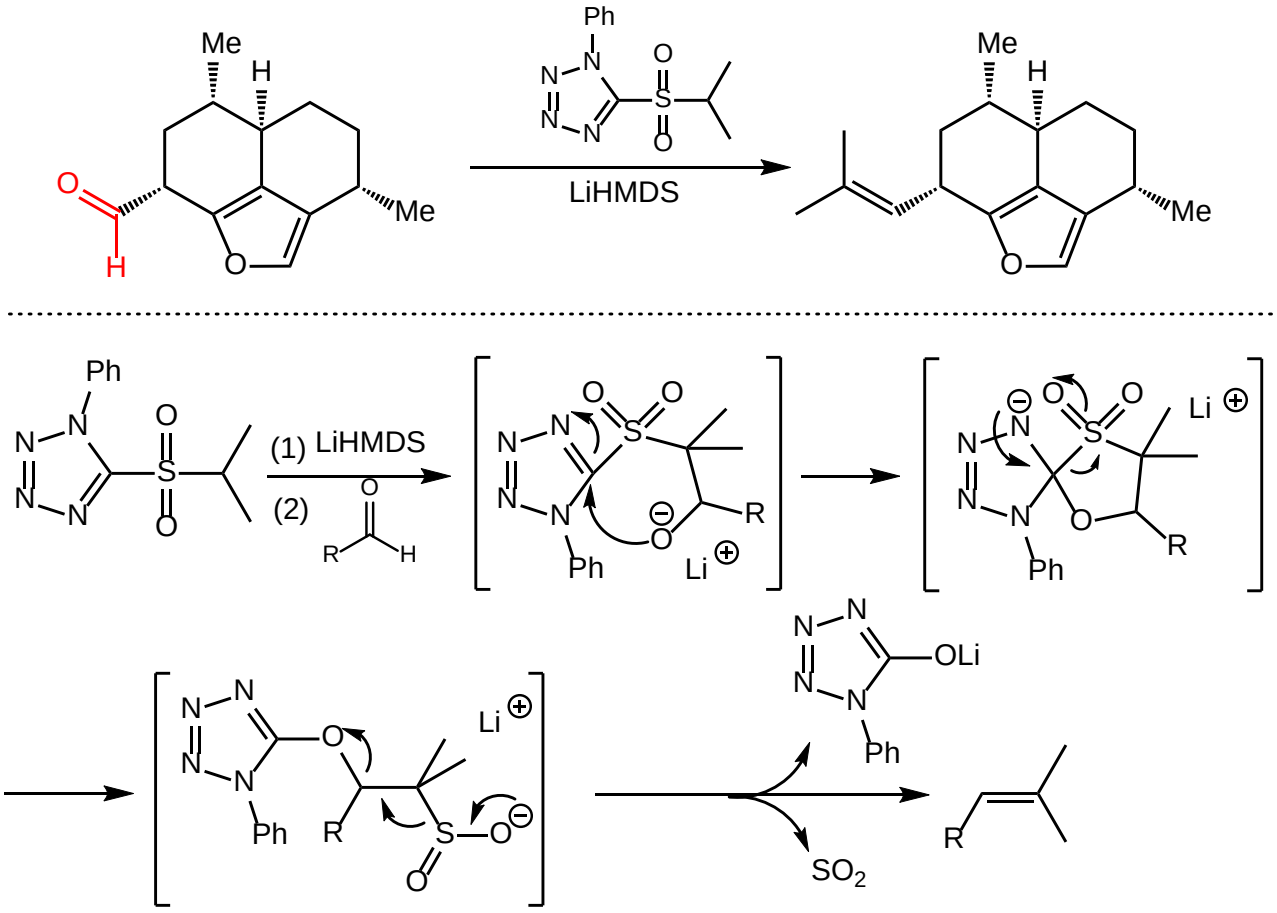


Total synthesis of Caribenol B

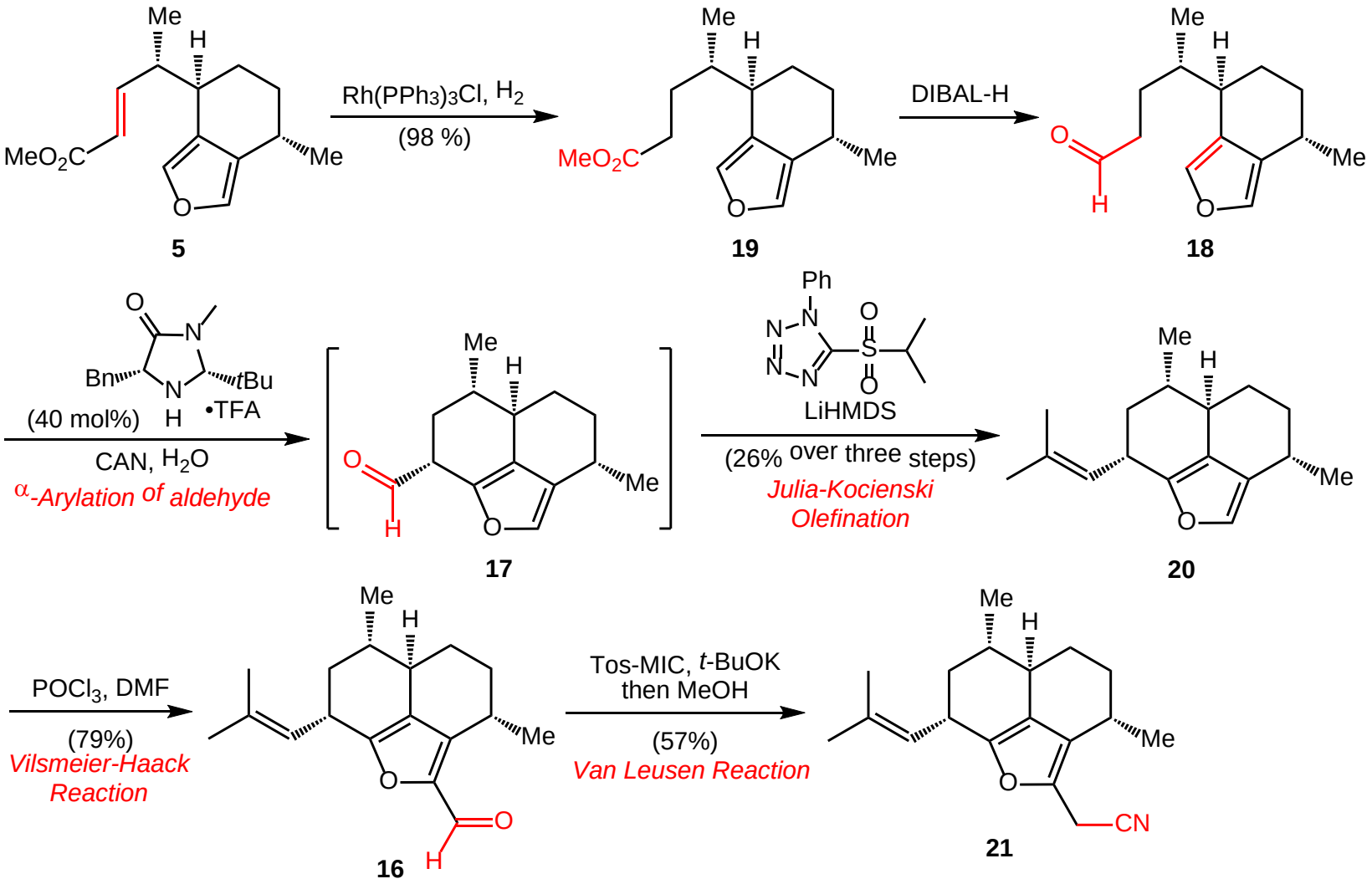


Julia–Kocienski olefination

The Julia Olefination enables the preparation of alkenes from 1-phenyl-1H-tetrazol-5-yl sulfone and aldehydes in a single step.

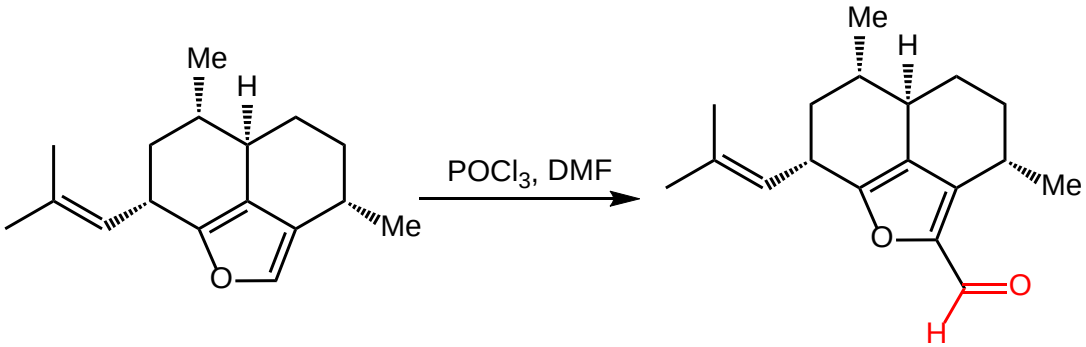


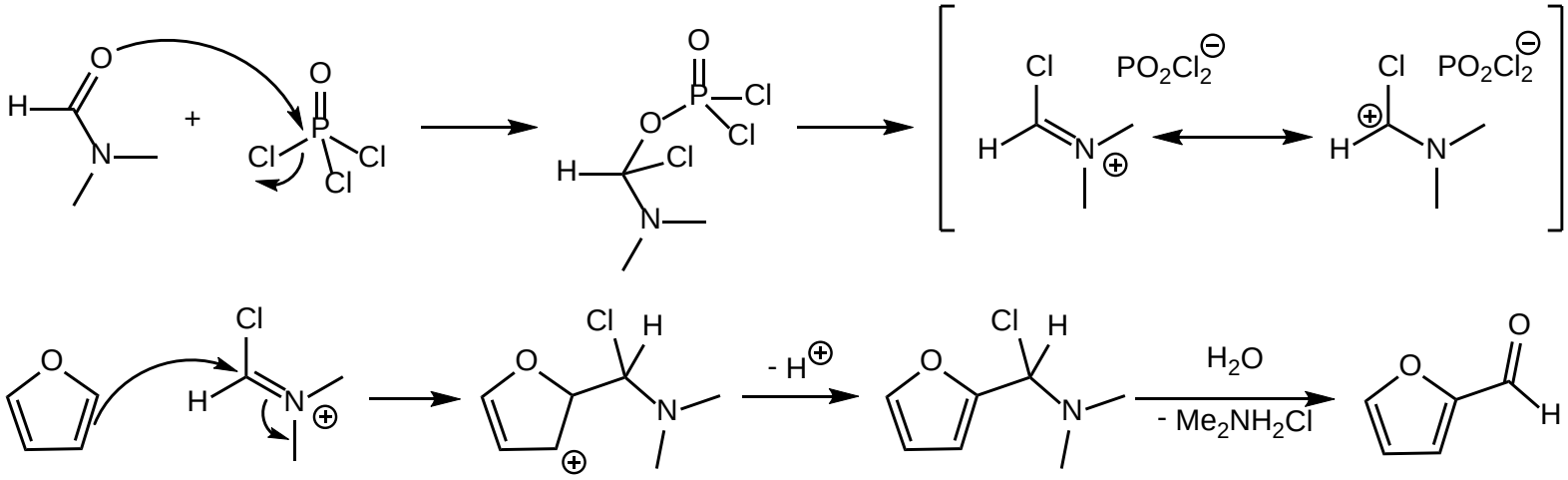
Total synthesis of Caribenol B



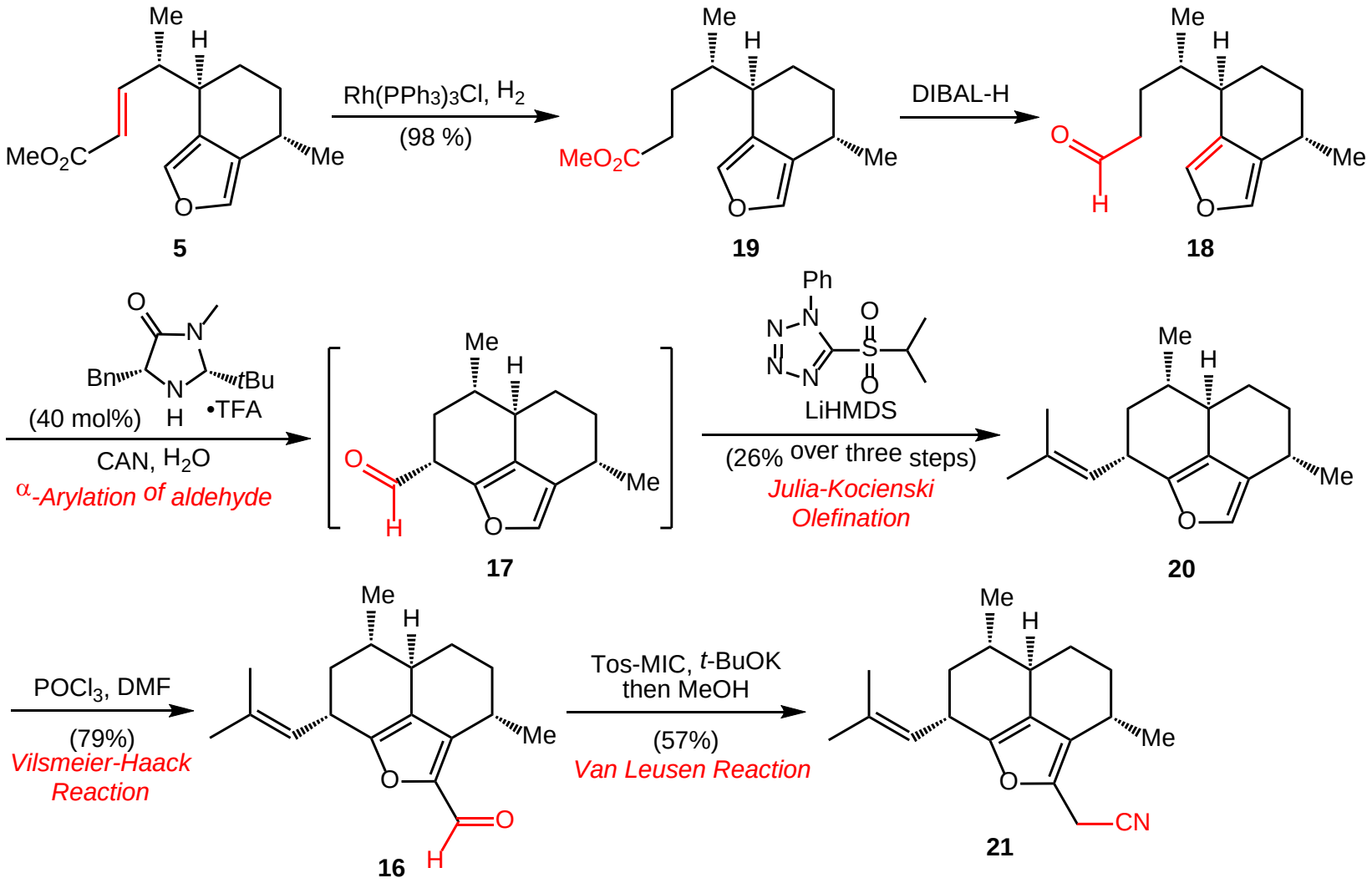
Vilsmeier-Haack Reaction

The Vilsmeier–Haack reaction is the chemical reaction of a substituted amide with phosphorus oxychloride and an electron-rich arene to produce an aryl aldehyde or ketone .



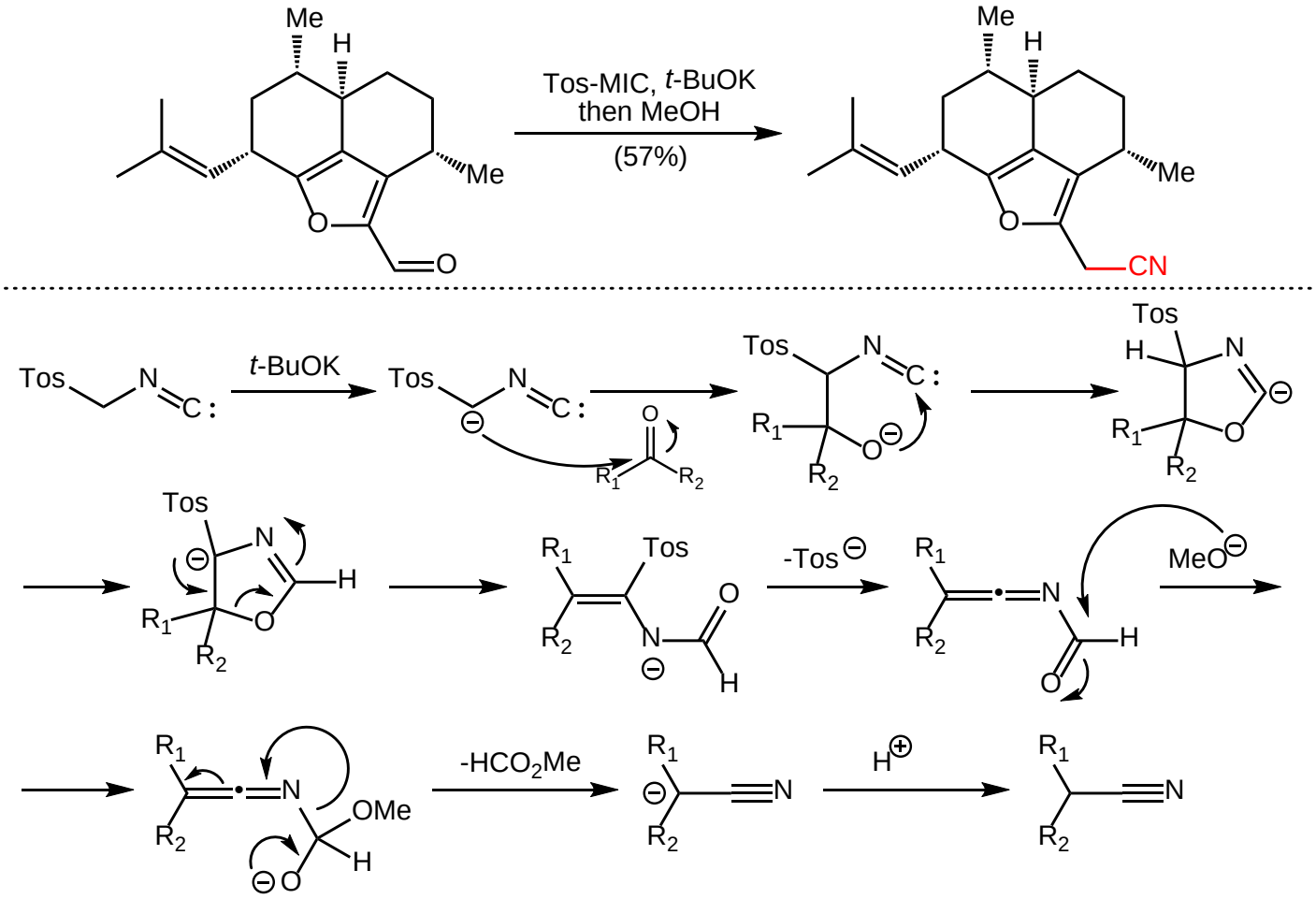


Total synthesis of Caribenol B

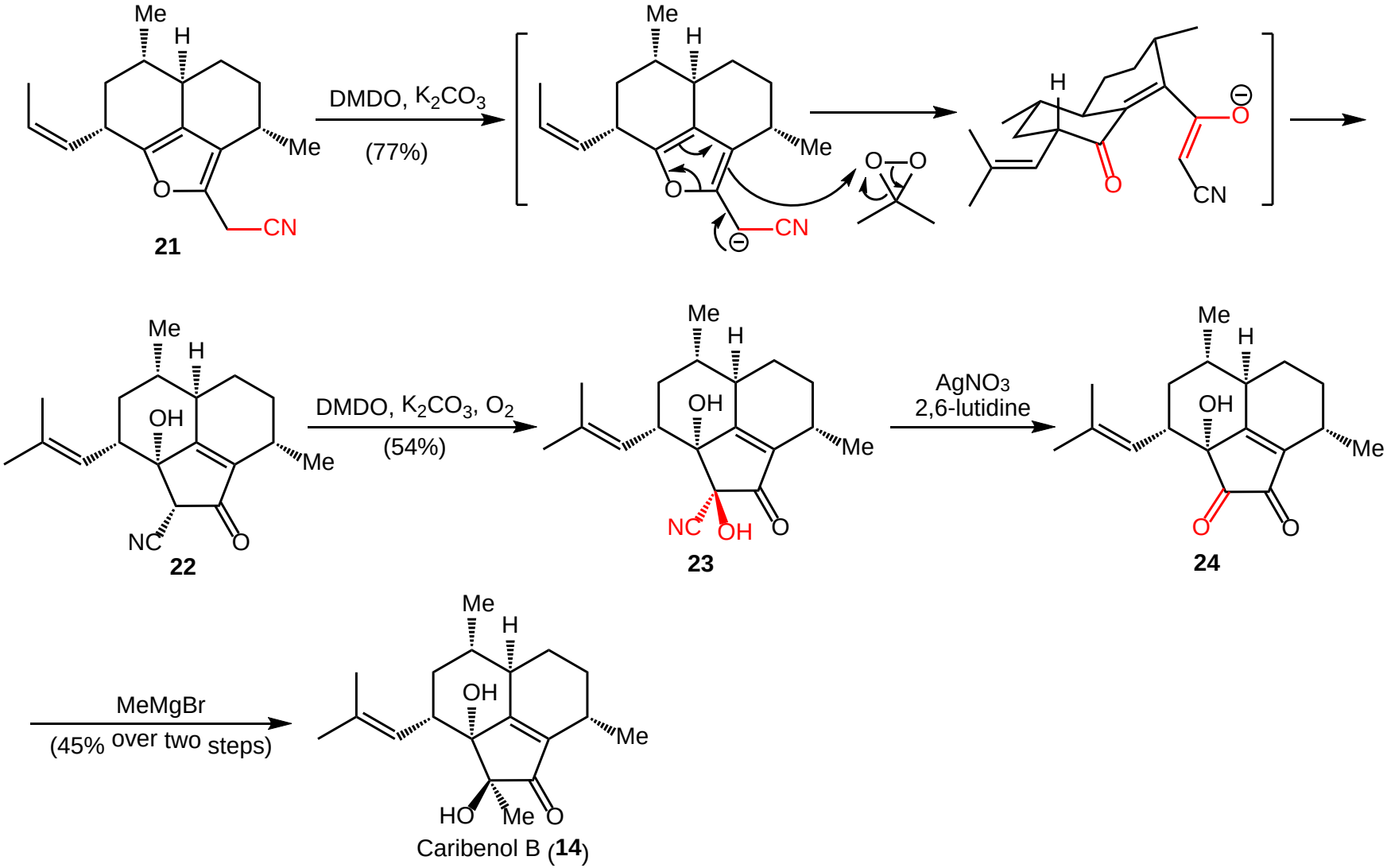


Van Leusen Reaction

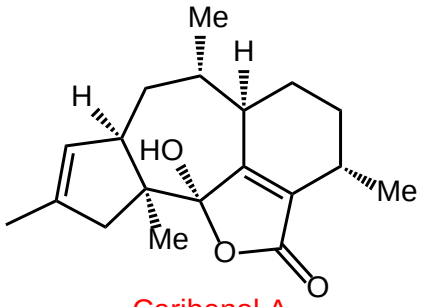
The Van Leusen Reaction allows the conversion of a ketone into a nitrile with one additional carbon atom in a single pot.



Total synthesis of Caribenol B



Summary



Caribenol A

- 17 Steps, 14% overall yield;
- The first total synthesis of Caribenol A;
- IMDA reaction;
- Furan oxidation.

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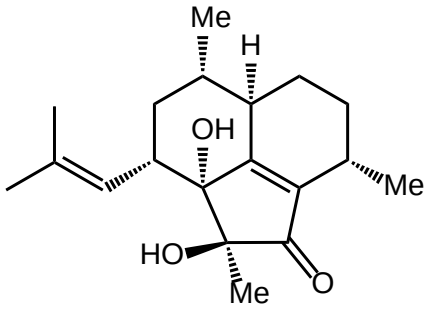

Caribenol B

- 17 Steps, 1.3% overall yield (Caribenol A);
- 12 Steps, 1.9% overall yield (Caribenol B);
- The first total synthesis of Caribenol B;
- Highly stereoselectivity and protecting group free;
- Friedel−Crafts triflation;
- Intramolecular organocatalytic *α*-arylation.

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The first paragraph

Furans teeter on the edge of aromaticity and can behave both as arenes and as very electron-rich dienes. As such, they can undergo a wide variety of chemical transformations, including electrophilic substitutions, metalations, cycloadditions, and oxidations. If extended to furyl carbinols, their synthetic power is increased even more, allowing for Piancatelli rearrangements and Achmatowicz reactions with subsequent cycloadditions to access carbocyclic systems. Often associated with a significant increase in molecular complexity, these transformations have been extensively exploited in the total synthesis of complex target molecules.

The last paragraph

In summary, we achieved an asymmetric synthesis of caribenol A and the first total synthesis of caribenol B. Both of our syntheses are highly stereoselective and protecting group free. The nucleophilicity of furans was critical to the success of our program, as they were used in a Friedel−Crafts triflation and an intramolecular organocatalytic *α*-arylation. A novel strategy for the conversion of furfurals into cyclopentenones and a mild method for the hydrolysis vinyl triflates were also developed. The scope of the gold-catalyzed cycloisomerization shown in Scheme 3 is under active investigation in our laboratories, and results will be reported in due course.

Acknowledgement

Thanks
for your attention