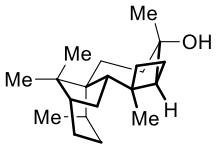
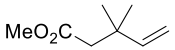
Harziane Diterpenoid

Total Synthesis and Structural Revision of a Harziane Diterpenoid
M. Hönig, E. M. Carreira, *Angew. Chem. Int. Ed.* **2020**, 59, 1192-1196.



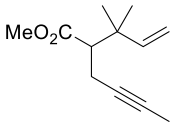
Harziane Diterpenoid

- Secondary metabolite of trichoderma fungi
- Antifungal, cytotoxic, anti-HIV and anti-inflammatory activity
- Unprecedented and highly caged 6-5-7-4 skeleton
- 6 contiguous stereocenters
- 3 quaternary carbon atoms
- Au-catalyzed diastereoselective cycloisomerization to install the cyclobutane core



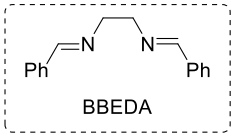
1

Reagents?



2

Mechanism

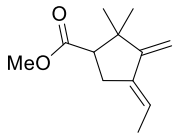


BBEDA

$Pd(OAc)_2$ (20 mol%)
BBEDA (20 mol%)
PhH, 79%

1) $Me(MeO)NH \cdot HCl$
MeMgCl, THF, 91%

2) $HOCH_2CH_2OH$
PPTS (10 mol%)
$HC(OMe)_3$, 78%



3

1) $BH_3 \cdot THF$ (4.0 eq.), THF
then NaOH, H_2O_2, 63%

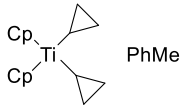
2) PivCl, Pyr, DCM
3) DMP, $NaHCO_3$,
76% (2 steps)

4

5 **> 4:1 dr**

Name of the reagent

1)



PhMe

2) $LiAlH_4$, 52% (2 steps)

6

1) TPAP (5 mol %), NMO,
DCM, 93%
2) K_2CO_3, MeOH
then Ohira-Bestmann
reagent, 87%

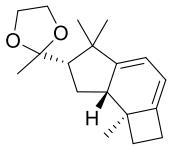
epimerization of one center

Name of the reaction
Machanism
Reagent structure
Name of the reaction
Mechanism

7

Mechanism

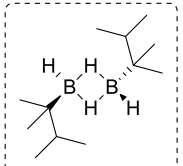
$Ph_3PAuNTf_2$ (3 mol%)
DCM, 87%, >11:1 dr



8

1) thexylborane (1.5 eq.),
THF, then NaOH, H_2O_2, 70%

2) TPAP (5 mol%), NMO,
DCM, 83%



Thexylborane

9

Name of the reagent
Mechanism

1) Et_2AlCN, PhMe

2) NaHMDS, THF, then Comin's reagent, 87% (2 steps)

9

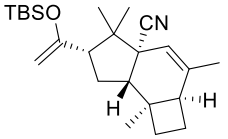
Structure of the Comin's reagent

10

1) $Pd(PPh_3)_4$ (5 mol%), $ZnMe_2$, THF, 86%

2) PPTS, acetone-H_2O (9:1), 81%

3) TBSOTf, 2,6-lutidine, DCM, 0 °C, 80%

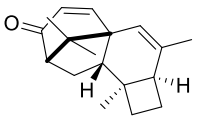


11

Mechanism

DIBAL-H (3 eq.), DCM, then aq. NaOH, silica gel

71%



12

1) CuI, MeLi, ether, then $BF_3{\cdot}OEt_2$, then **12**, 89%

2) $RuCl_3.xH_2O$ (20 mol%), $NaIO_4$, DCE-H_2O (5:4), 65%

13

1) LiHMDS, THF

2) $Ph_3P{=}CH_2$, THF, 79% (2 steps)

3) DIBAL-H (3.0 eq.), DCM, 93%

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Name of the reaction

1) CS_2, KHMDS, THF, then MeI, 91%

2) AIBN (38 mol%), Bu_3SnH, PhH, 89%

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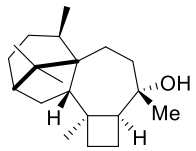
Name of the reagent
Mechanism

$Co(acac)_2$ (18 mol%), O_2, $PhSiH_3$, THF, 83%



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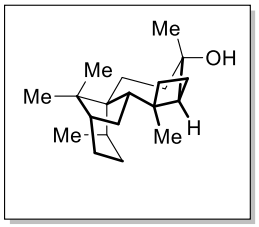

Solutions

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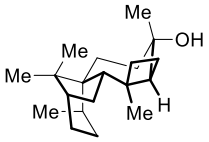

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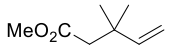
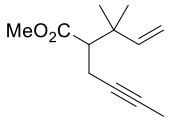


1

LDA, THF,
then 1-bromobut-2-yne
97%



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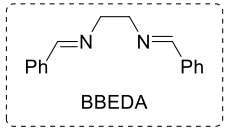

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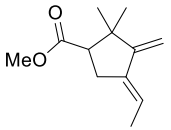

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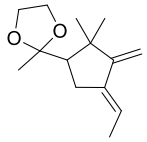

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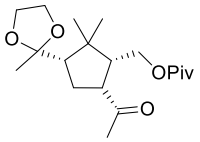

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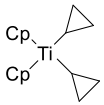
1) 
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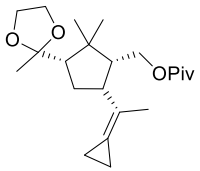

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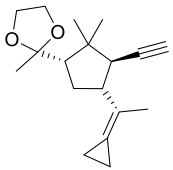
Name of the reaction
Machanism
Reagent structure
Name of the reaction
Mechanism



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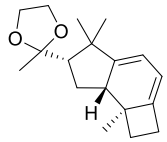

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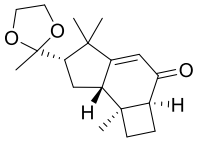

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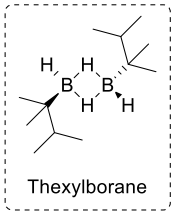

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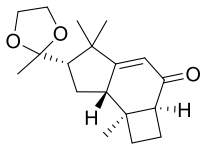

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Mechanism

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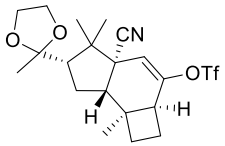
Structure of the Comin's reagent



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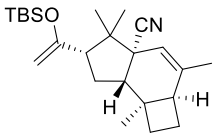

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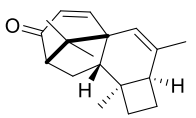

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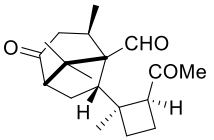

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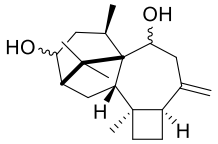

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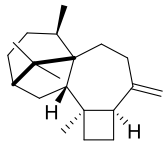

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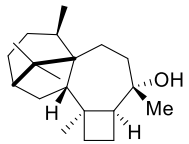

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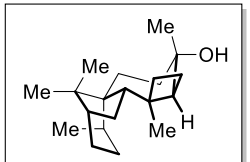

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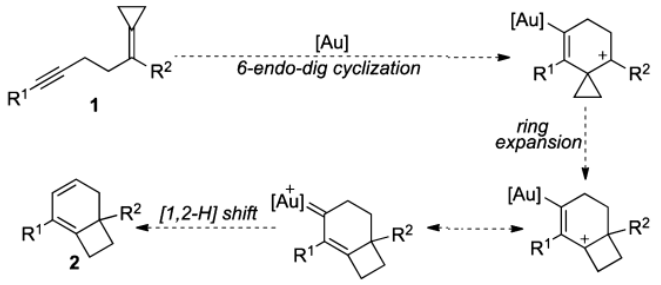
Key step: Au-catalyzed diastereoselective cycloisomerization



H. Zheng, R. J. Felix, M. R. Gagné, *Org. Lett.* **2014**, 16, 2272 – 2275.