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Communication

# Asymmetric Total Synthesis of the Highly Strained $4\beta$ -Acetoxyprobotryane- $9\beta$ , $15\alpha$ -diol

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# **Structural features:**

Strained trans bicyclo[3.3.0]octane

**7** Contiguous stereocenters:

two vicinal quaternary

No total synthesis reported

**4** $\beta$ -acetoxyprobotryane-**9** $\beta$ ,**15** $\alpha$ -diol (6)





J. Am. Chem. Soc. 2017, 139, 5007.

Scheme 1. Retrosynthetic Analysis of  $4\beta$ -Acetoxyprobotryane- $9\beta$ ,  $15\alpha$ -diol (6)







### **Eschenmoser-Tanabe-type fragmentation**

Synthesis of cyclic alkynones:





**R** = tosyl, 2,4-dinitrophenyl;  $R^{1-2} = H$ , alkyl; when  $R^2 = H$ , then the product is an alkynal, and when  $R^2 = alkyl$ , then it is an alkynone







Angew. Chem. Int. Ed. 2018, 57, 8744.



<sup>*a*</sup> Reagents and condition: (a) Supporting Information and ref 4; (b) IBX, DMSO, 85 °C, 72%; (c)  $H_2O_2$ , NaOH,  $H_2O$ -MeOH, 0 °C, 88%; (d)  $H_2NCONHNH_2 \cdot HCl$ , NaOAc,  $H_2O$ -EtOH, rt, 89%; (e) Pb(OAc)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -10 °C, 60%; (f) NaBH<sub>4</sub>, MeOH, 0 °C, 87%; (g) *o*-iodoaniline, Pd(PPh<sub>3</sub>)<sub>4</sub>,

J. Am. Chem. Soc. 2010, 132, 1236.





## **Copper-Catalyzed Cross-Coupling of Diazo Compounds with Terminal Alkynes**



**Scheme 1** Copper-catalyzed cross-coupling of diazo compounds with terminal alkynes

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#### **Transition Metal-Mediated [4+2] Cycloaddition Reactions**

electronically dissimilar diene and dienophile



Chem. Rev. 1996, 96, 49.

# Electronically similar diene and dienophile (electronically neutral dienes and dienophiles)





Org. Lett. 2016, 18, 4932.





Rh

[Rh(ethylene)<sub>2</sub>Cl]<sub>2</sub>

(17)

Ph

Ρh

Ph

*i*-Pr

CL

NHC

(L7)

*i-*Pr *i-*Pr

(S,R,R)-PN (L2)

(S,S)-Ph-Bod

(L4)

*i-*Pr

Me

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Figure 1. Plausible reaction mechanism.

J. Am. Chem. Soc. 2006, 128, 12648.

a) Rationale for the stereochemical outcome of rhodium-catalyzed [4+2] cycloaddition









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X = p -toluenesulfonate (TsO) or (1S) -(+) -10-Camphorsulfonate (CsO).

J. Org. Chem. 1991, 56, 6110.

# **Benzilic acid rearrangement** P52



#### Mechanism:







# Summary

- Achieved the first and asymmetric total synthesis of the highly strained 4β-acetoxyprobotryane-9β,15α-diol (6) via a linear sequence of 14 steps
- The synthetically challenging [6-5-5] tricyclic ring system of 6 was synthesized via an asymmetric Rhodium-catalyzed [4 + 2] cycloaddition reaction, followed by a unique and very mild benzilic acid type rearrangement
- The first application of a chiral rhodium complexcatalyzed [4 + 2]
  reaction in natural product synthesis