

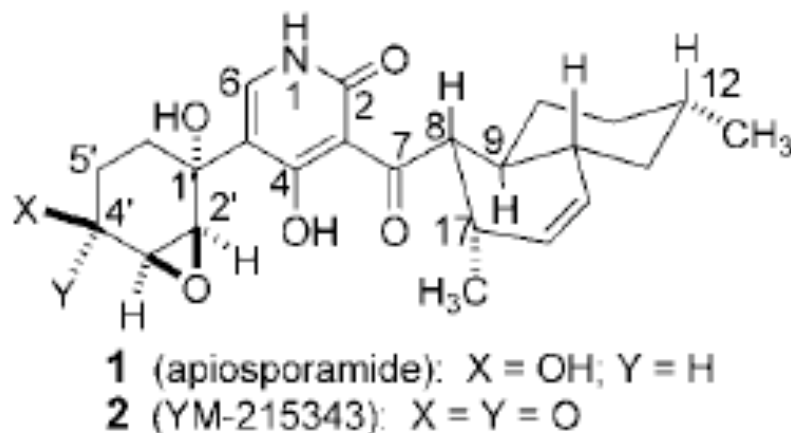
Total Synthesis of (+)-Apiosporamide

Angew. Chem. Int. Ed. **2005**, early view

Williams, David R.; kammler, D.C.,
Donnell, A. F.; Goundry, W. R. F.

By Chunrui
Oct 5, 2005

Bioactivity



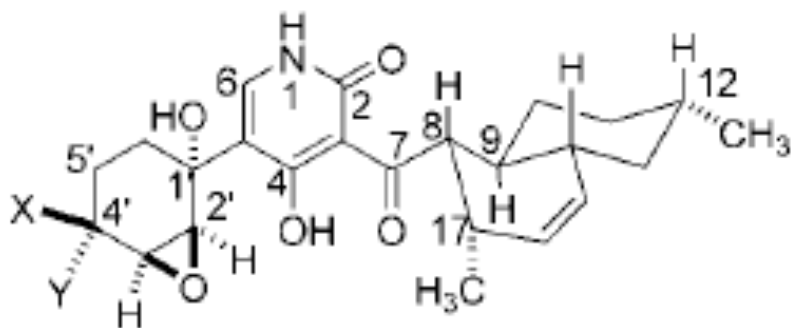
- Isolated from the fungus *Apiospora montagnei* in **1994**
- Antifungal activity against fungus *Ascobolus furfuraceus*
- Antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*

YM-215343

- isolated recently
- Cytotoxicity against HeLaS3 cell cultures

Alfatafta, A. A.; Gloer, J. B. *J. Nat. Prod* **1994**, 57, 1696

Structure I



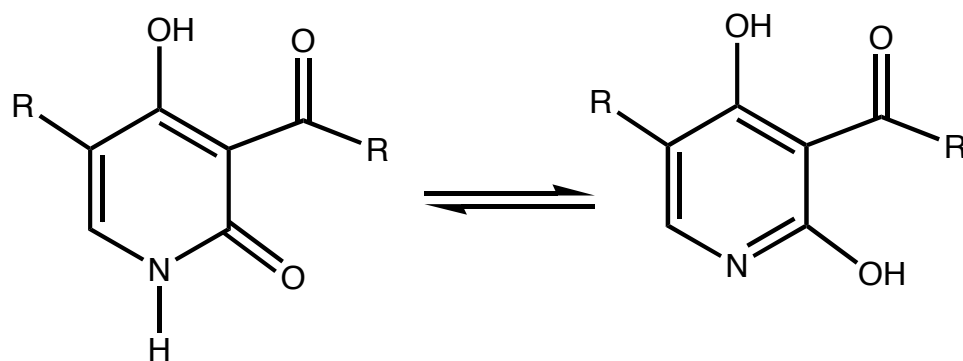
- 1** (apiosporamide): X = OH; Y = H
2 (YM-215343): X = Y = O

➤ ¹³C NMR in CD₃OD showed only 18 resonances, even with increased relaxation delays

➤ hrFABms: (M+H)⁺ m/z 430.2217

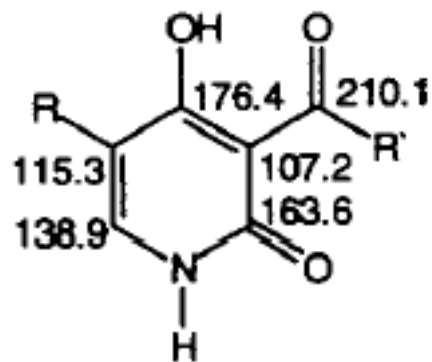
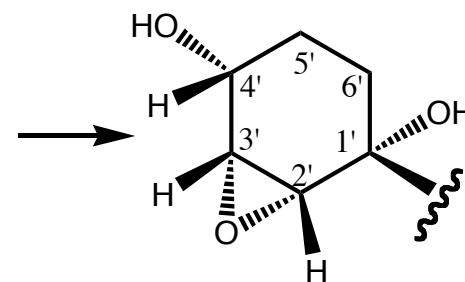
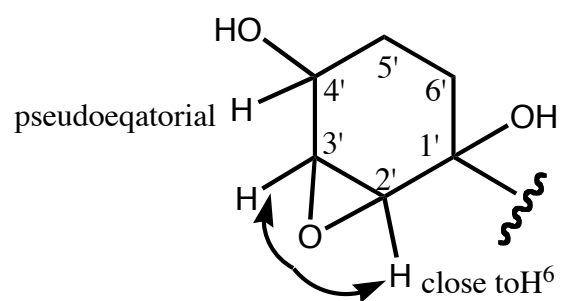
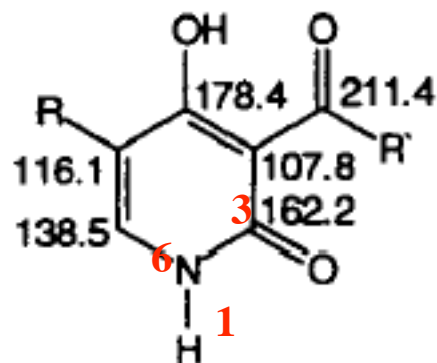
➤ HMBC showed correlations for which no corresponding resonances in ¹³C NMR

- ❖ ¹³C NMR in Me₂CO-d₆ showed 24 resonances
- ❖ 6 sp² carbon was missing in CD₃OD
- ❖ C₂₄H₃₁NO₆

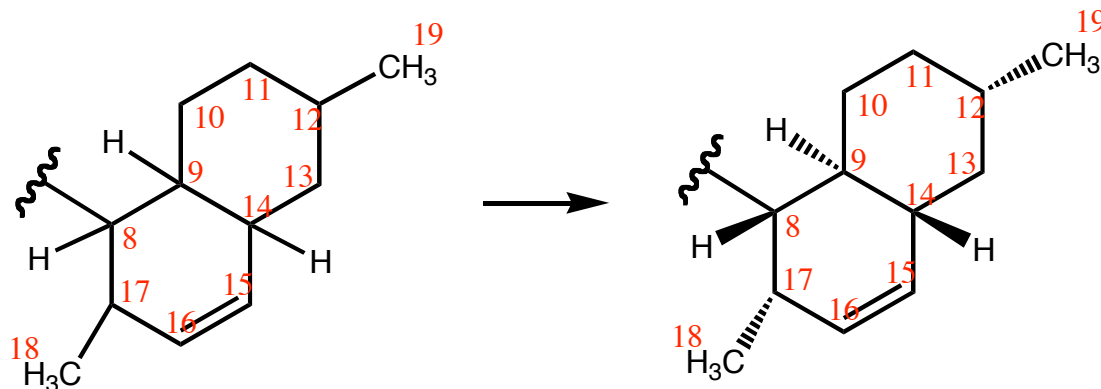


Alfatafta, A. A.; Gloer, J. B. *J. Nat. Prod.* **1994**, *57*, 1696

Structure II



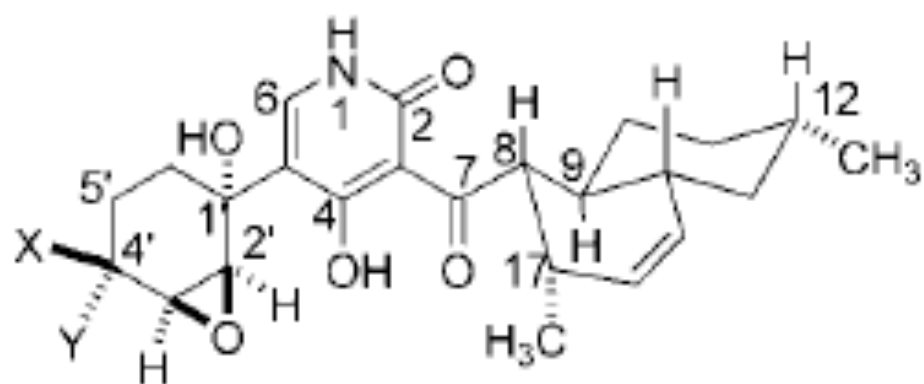
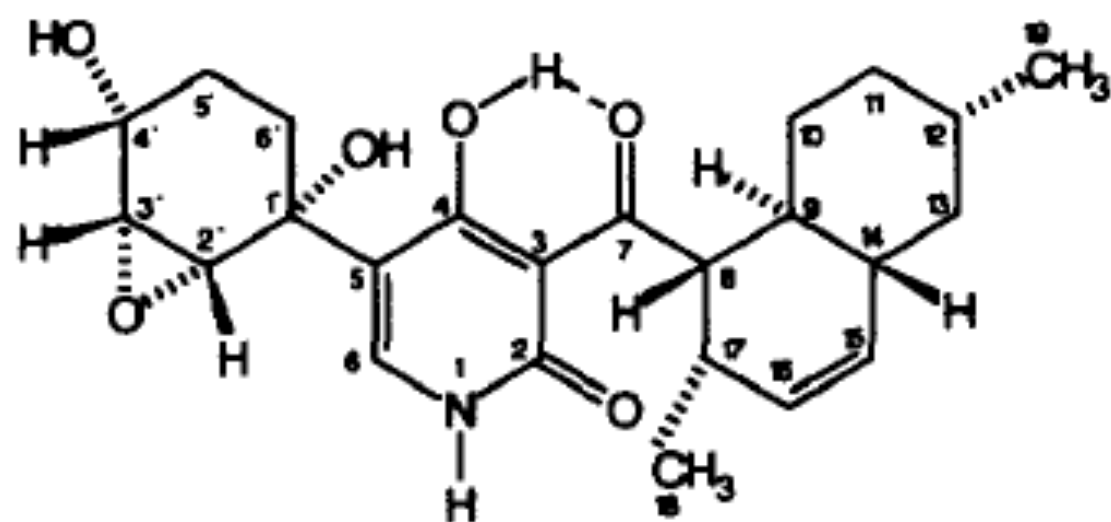
Ilicicolin H



NOSEY H⁸-H¹⁴ H¹⁸-H⁹, H⁹-H_{ax}¹¹, H_{ax}¹¹-H¹⁹, H¹⁴-H¹²

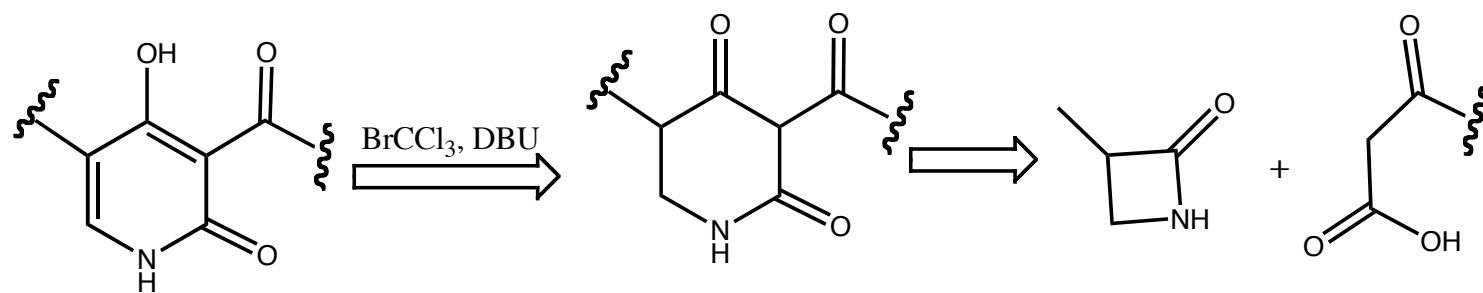
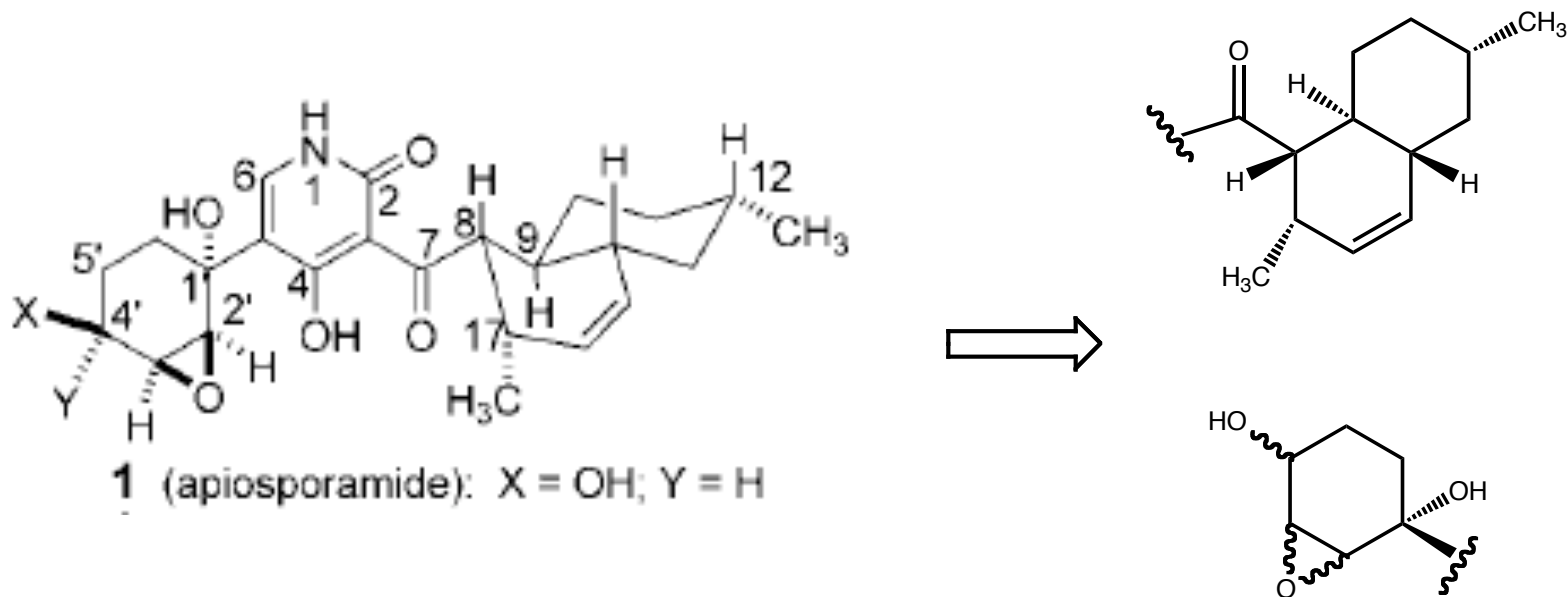
$J_{H^8-H^9} = 11$ Hz No NOSEY H⁹-H¹⁴

Alfatafta, A. A.; Gloer, J. B. *J. Nat. Prod.* **1994**, *57*, 1696

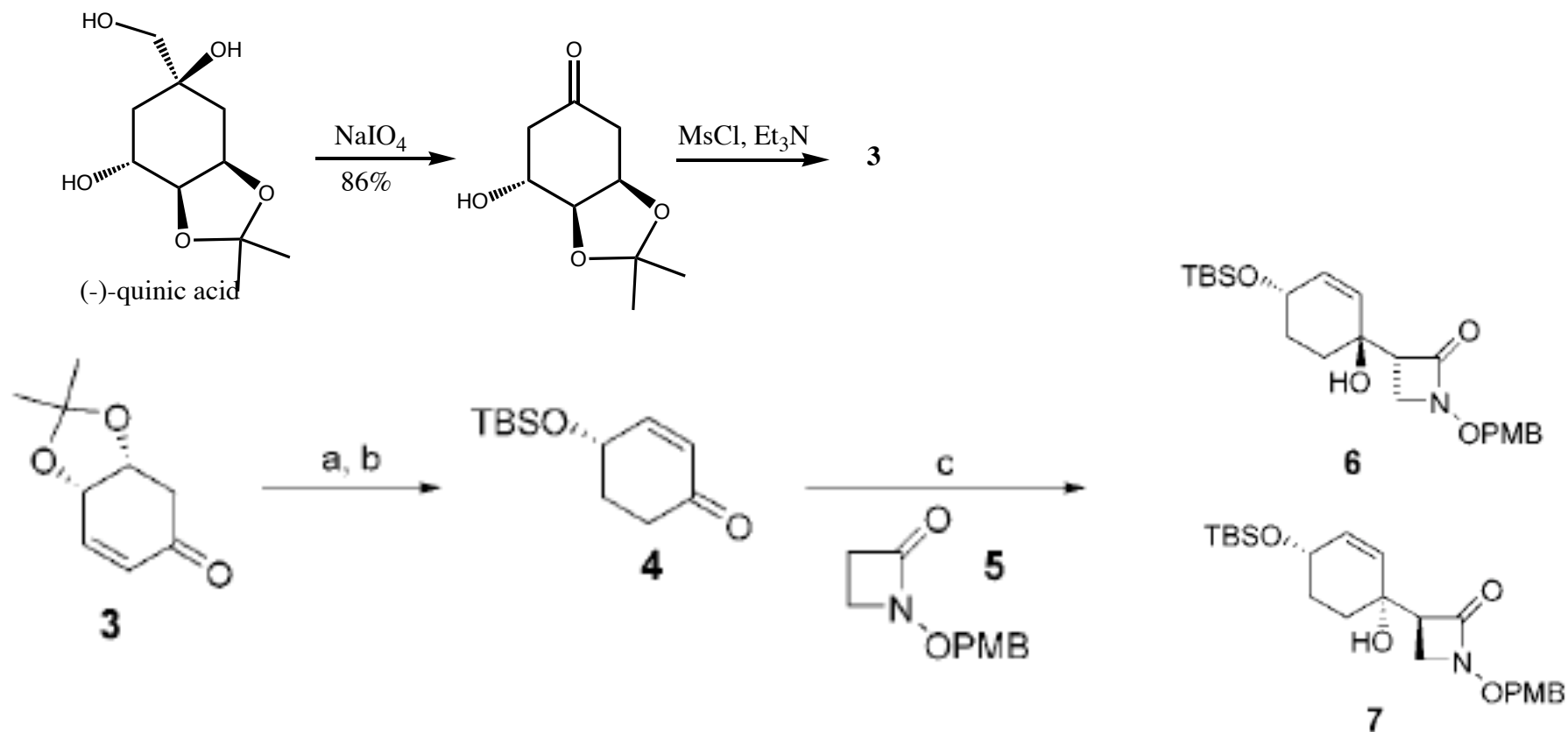


- 1** (apiosporamide): X = OH; Y = H
2 (YM-215343): X = Y = O

Retrosynthesis



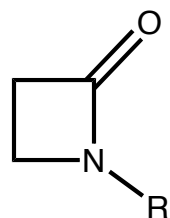
Synthesis of Epoxycyclohexanediol moiety



a) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, 97%; b) DBU , TBSCl , heat, 72%; c) KHMDS , THF , -78°C , 2 h; then **4** at -78°C ; 97%, (d.r. 1.6:1);

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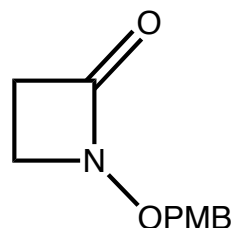
Addition of β -lactams



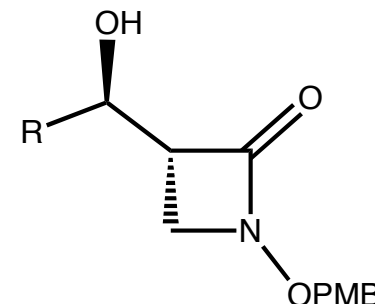
R = benzyl, silyl, 4-methoxy benzyl

Boron enolate: no reaction

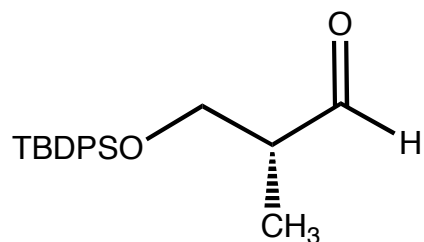
Mg, Sn, Zn: low selectivity and yield



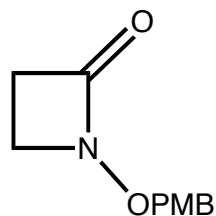
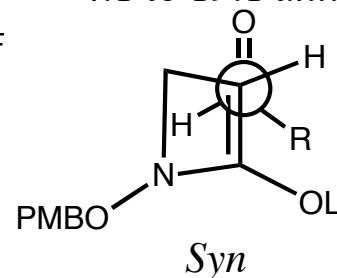
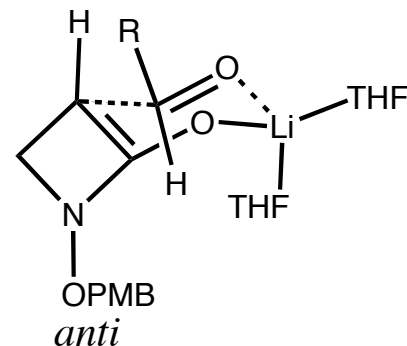
1) LHMDS, -78°C
2) RCHO



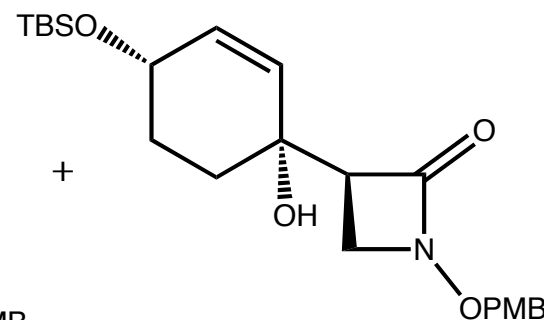
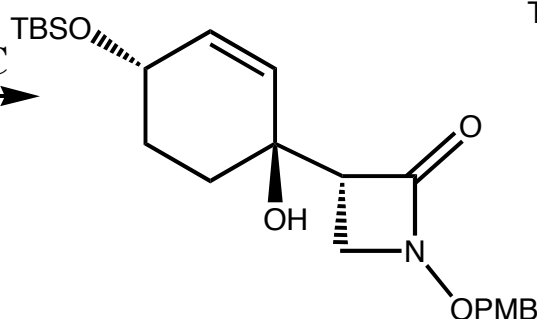
4:1 to 19:1 *anti*: *syn*



anti:*syn* 19:1
anti ratio 1.4:1

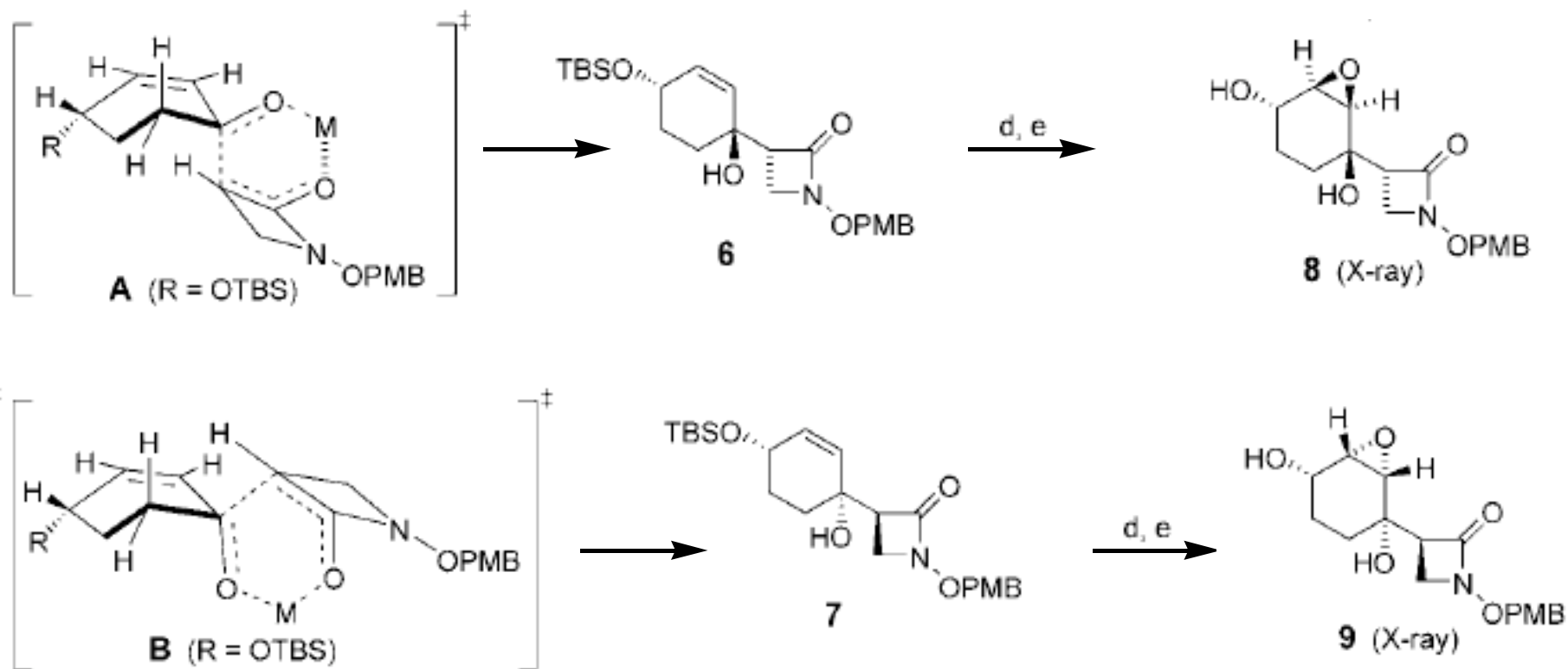


1) LHMDS, -78°C
2) TBSO-CH=CH-C(=O)-C₆H₁₀



Heterocycles **2004**, 62, 167 1.2 : 1 97%

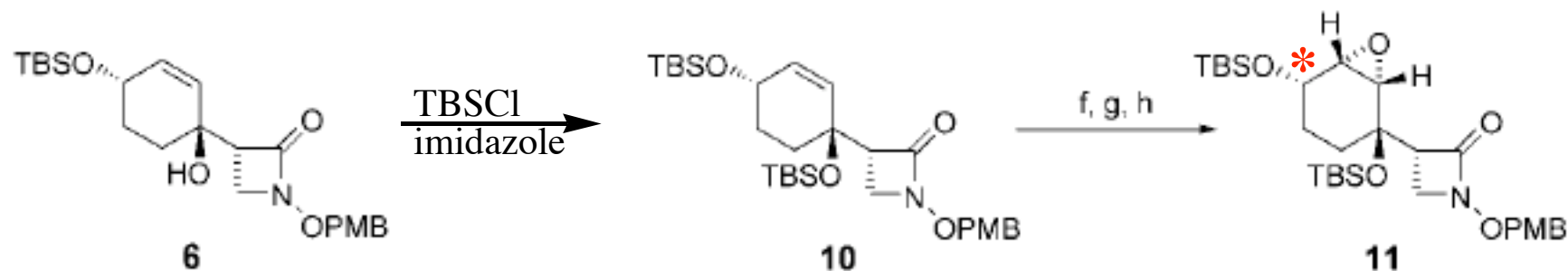
Synthesis of Epoxycyclohexanediol moiety



1); d) cat. $\text{Mo}(\text{CO})_6$, $t\text{-BuOOH}$, benzene/ CH_2Cl_2 (5:1 by v/v), 2 h; 66%; e) cat. aq. H_2SiF_6 , $\text{CH}_3\text{CN}/t\text{BuOH}$ (9:1 by volume), 22 °C, 80%;

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Diastereomers of Epoxycyclohexanediol moiety

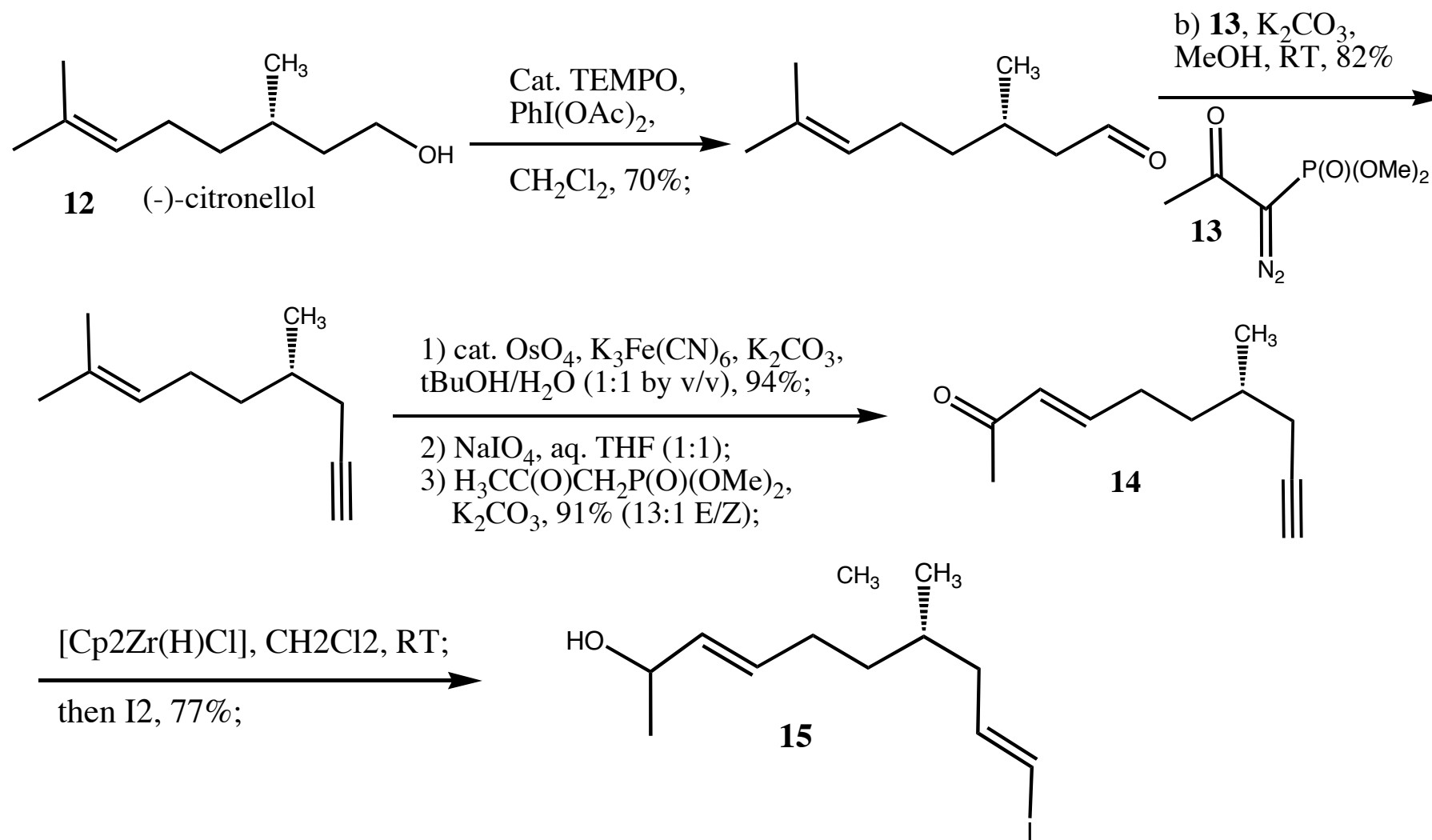


f) TBAF, 0°C, 98%;

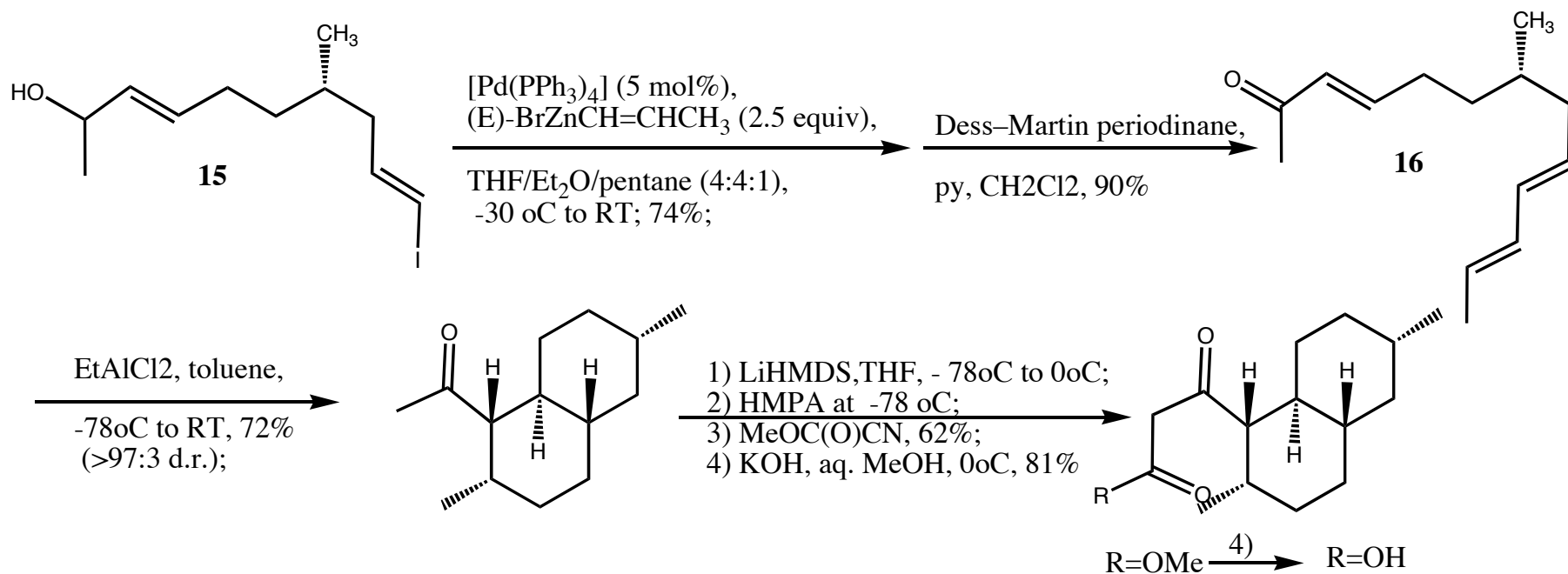
g) MCPBA, CH₂Cl₂, NaHCO₃, 54%;

h) TBSCl, imidazole, CH₂Cl₂, 100%.

Synthesis of Decalin moiety

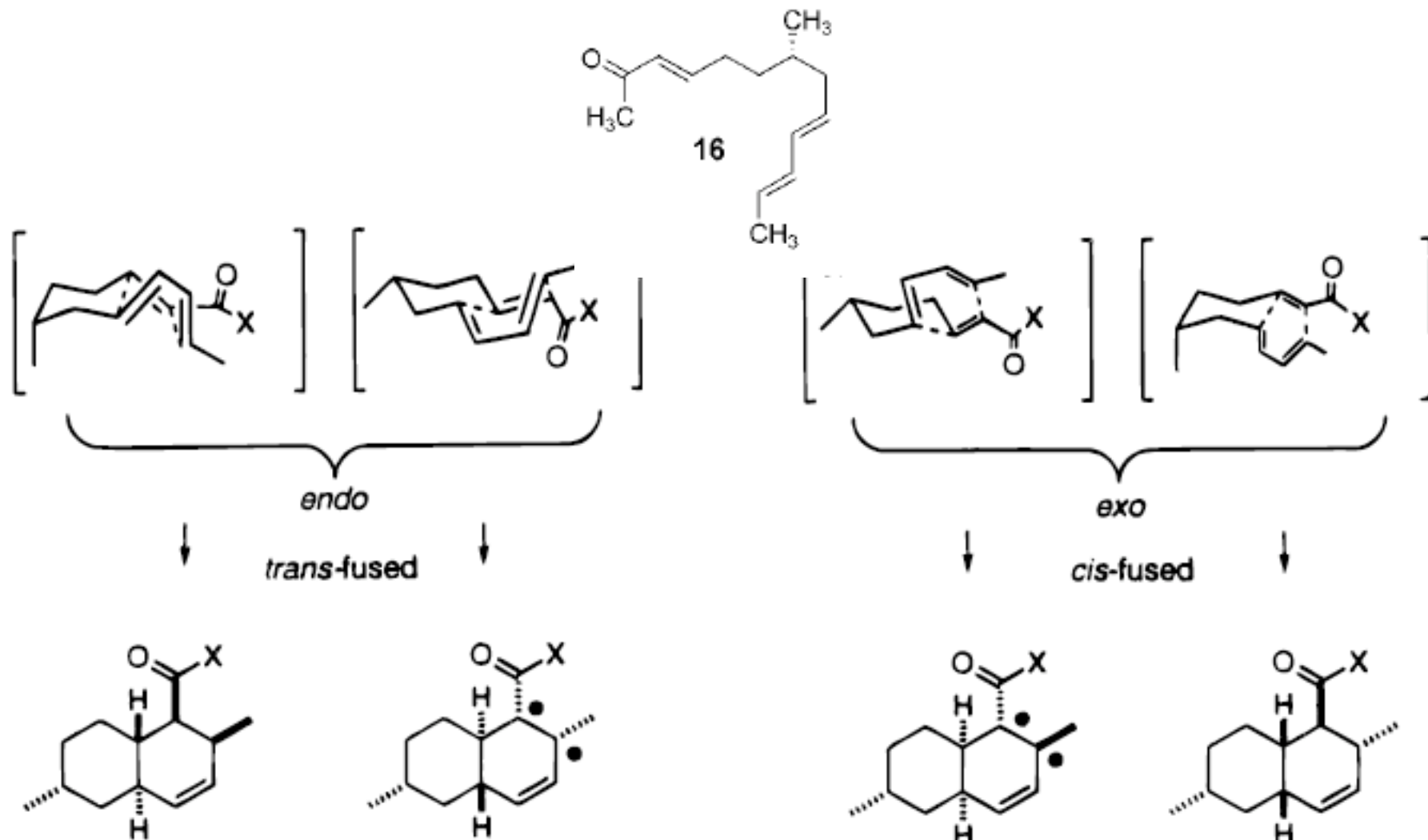


Synthesis of Decalin moiety



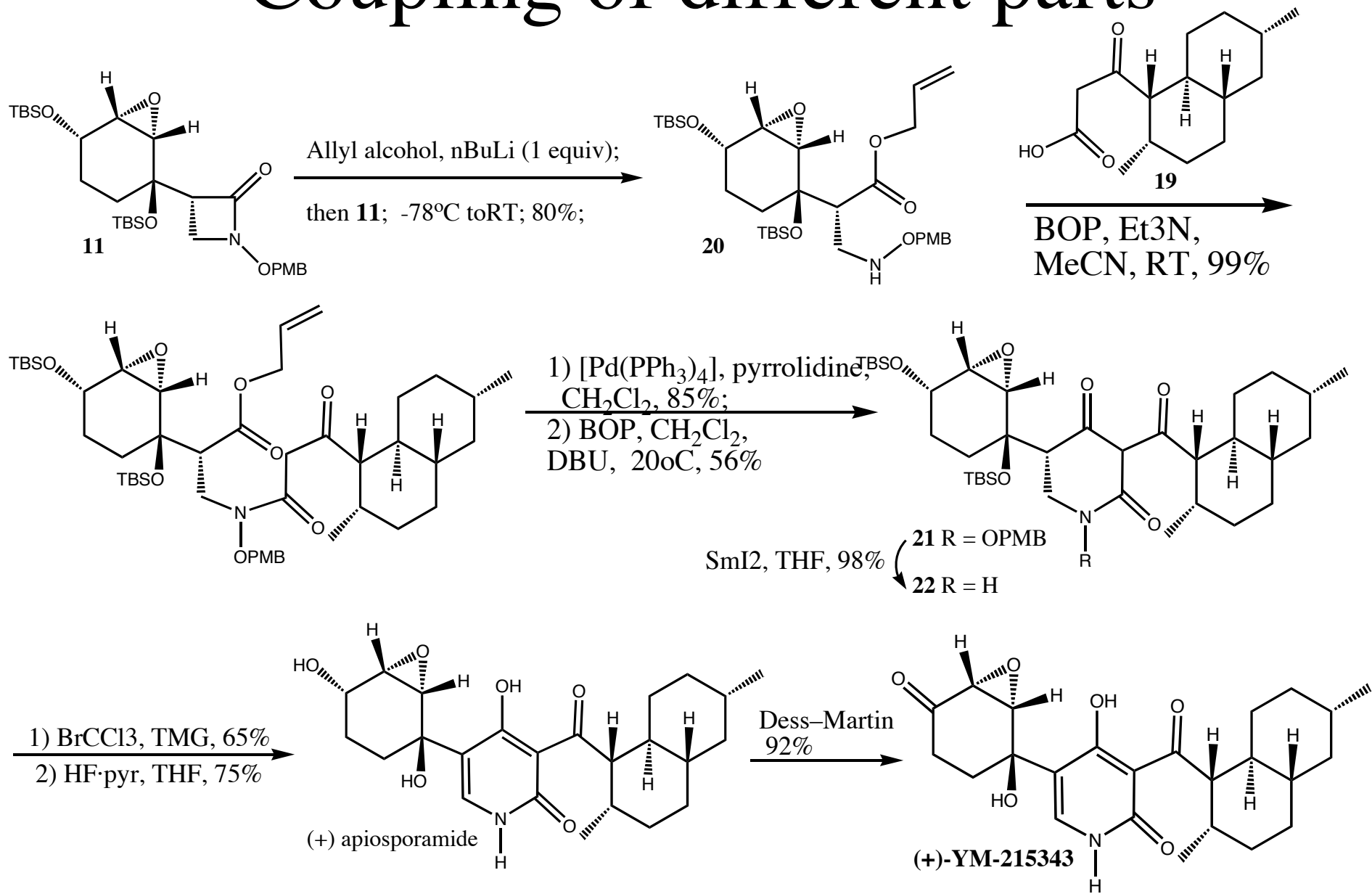
180 °C, toluene, 7:3 *d.r.*

Stereochemistry of Diels-Alder RXN

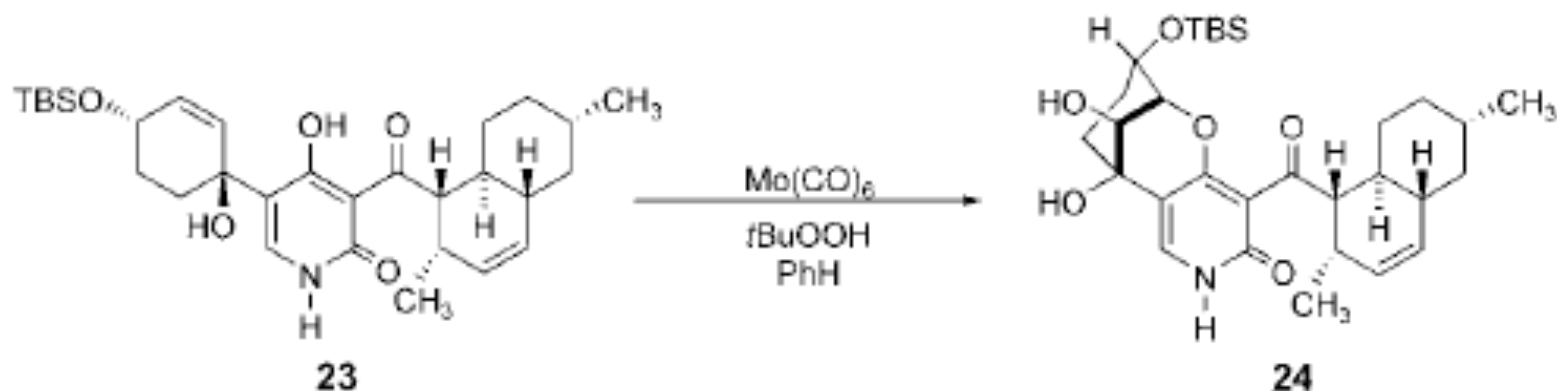


Witter, D. J.; Vederas, J.C. *J. Org. Chem.* **1996**, *61*, 2613

Coupling of different parts



Epoxidation of intermediate **23**



Oxidation of diastereomer **25**

