
Total Synthesis of Celastrol, Development of a Platform to Access Celastroid Natural Products

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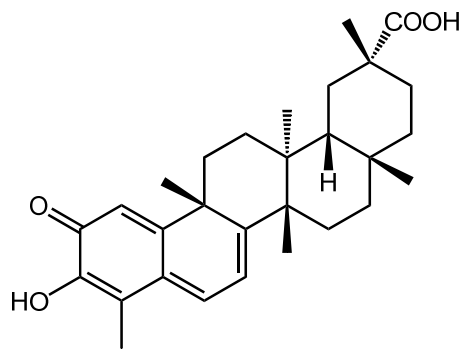


Siegel, D. *et al.* *J. Am. Chem. Soc.* **2015**, *137*, 11864.

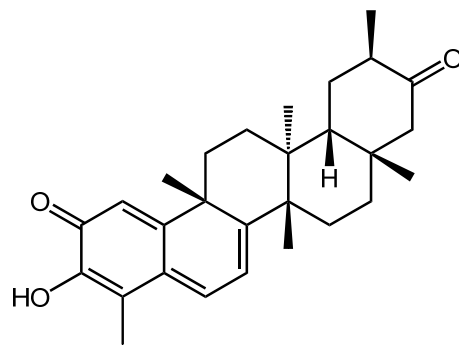
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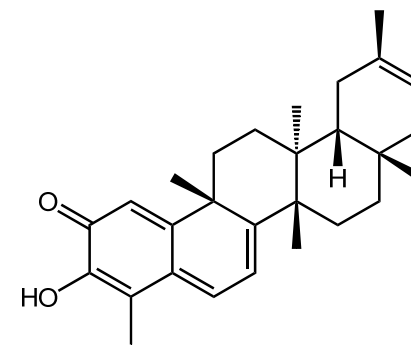
Introduction



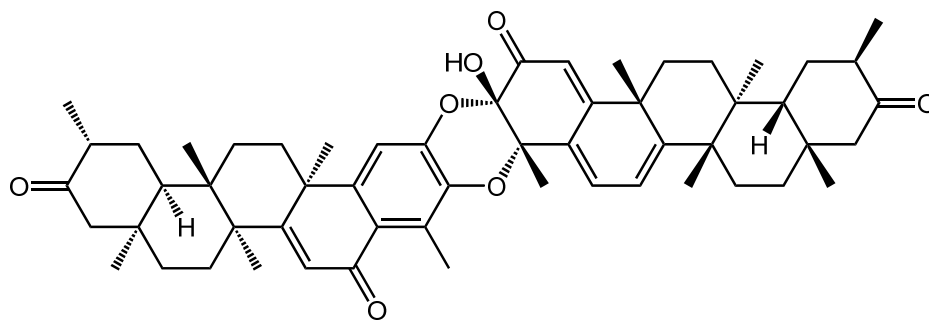
celastrol 1



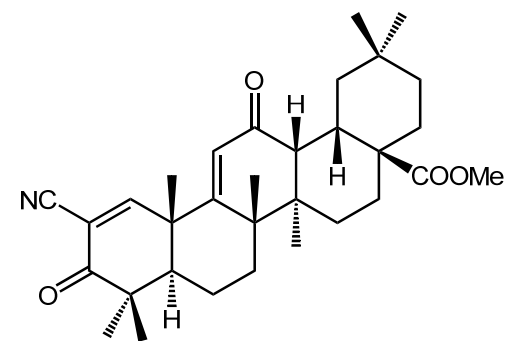
tingenone 2



iguesterin 3



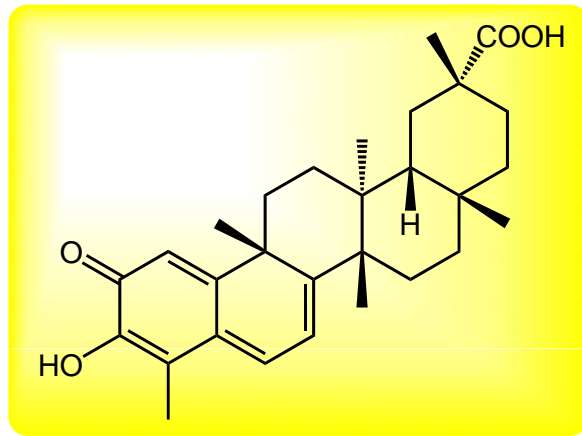
xuxuarine 4



CDDO methyl ester 5

De Santana, C. F. *Rev. Inst Antibiot. Recife* **1971**, *11*, 37.

Introduction



Celastrol

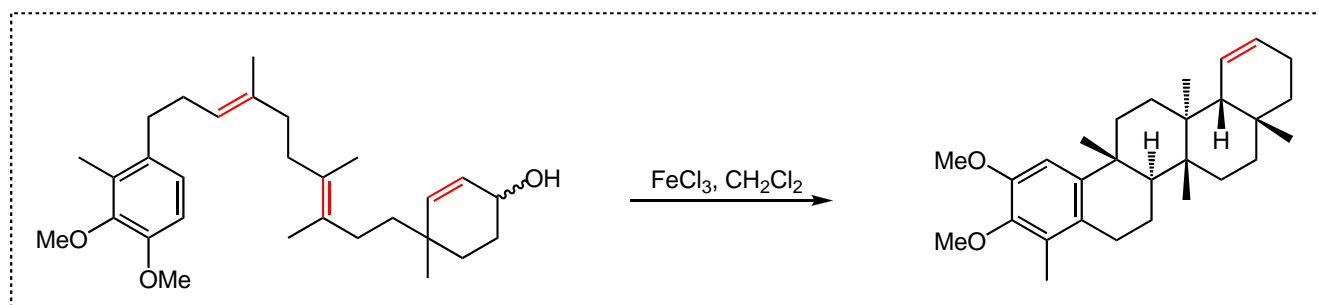
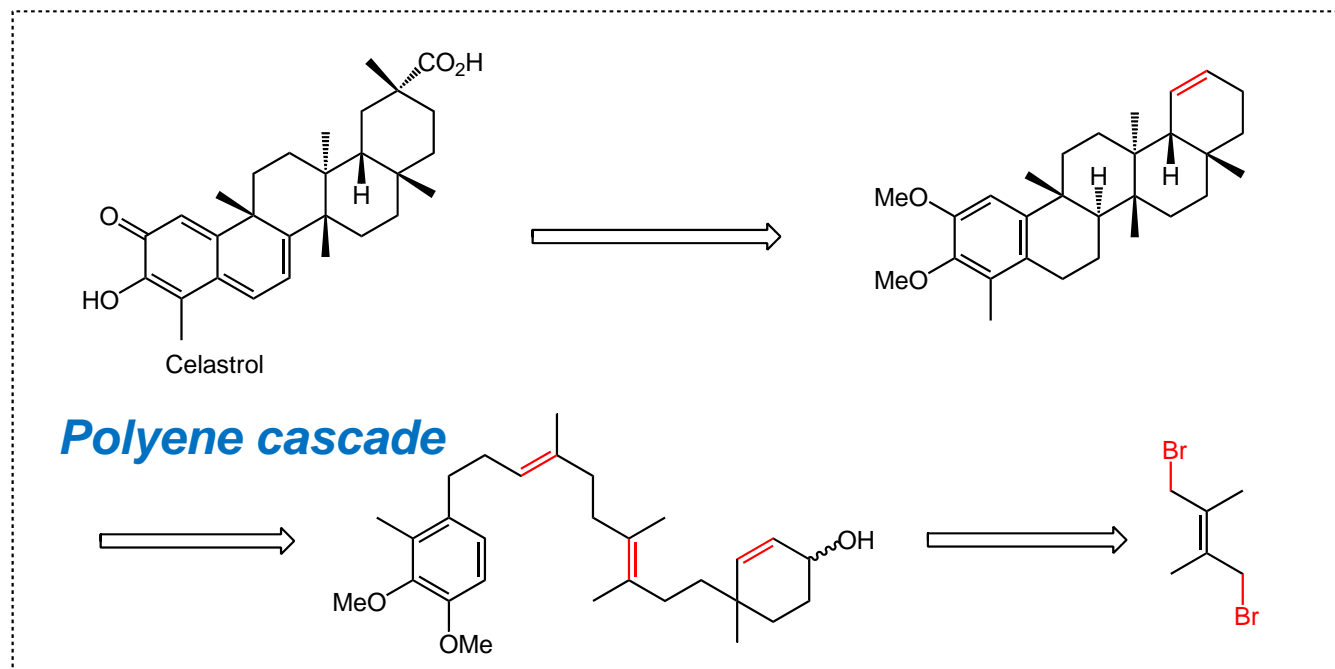


Tripterygium wilfordii

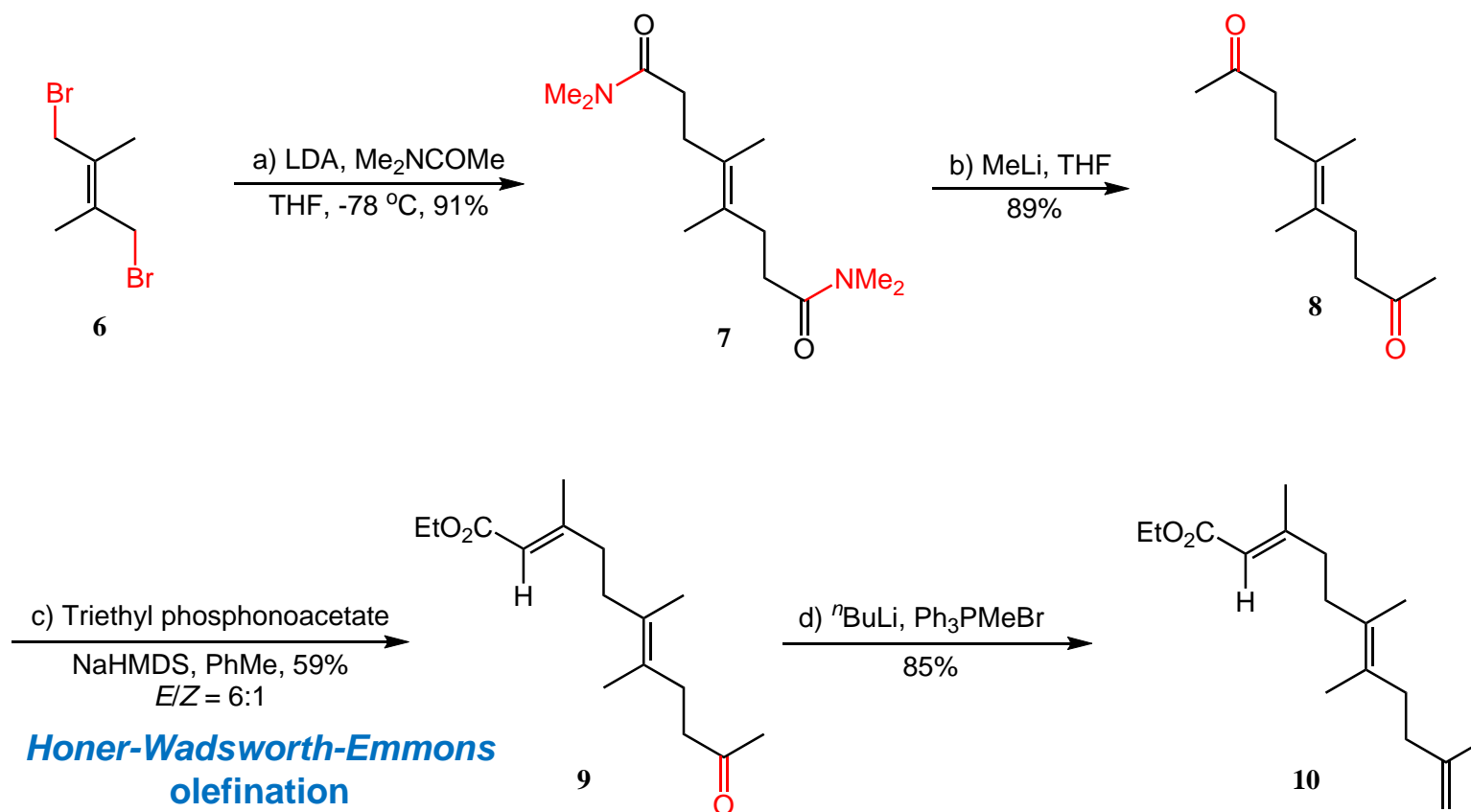
- ◆ Initially isolated from *Tripterygium wilfordii*
- ◆ Activities relevant to neuronal degeneration, inflammation

Kiaei, M. *et al. Neurodegener. Dis.* **2005**, 2, 246.

Retrosynthesis of Celastrol

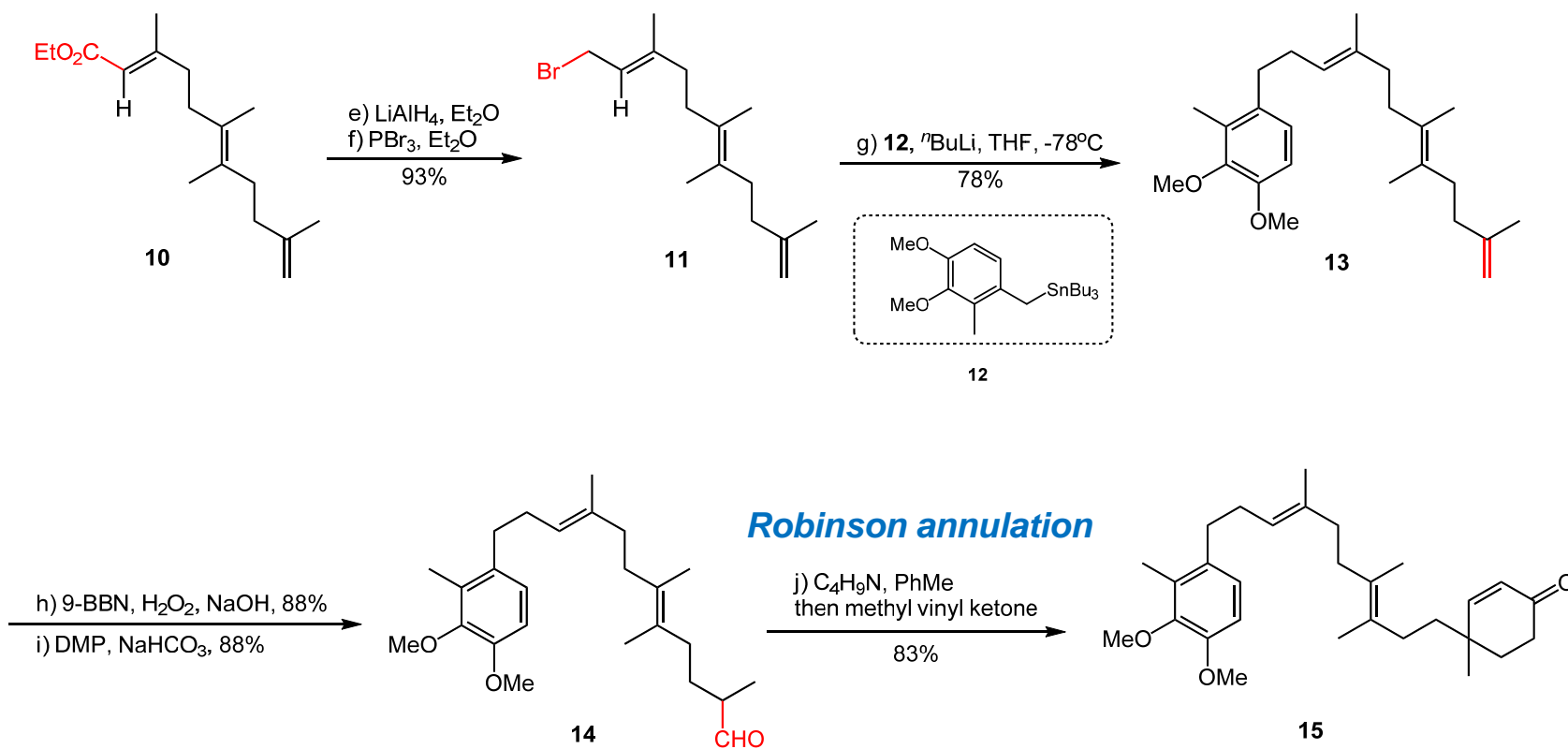


Total Synthesis of Celastrol



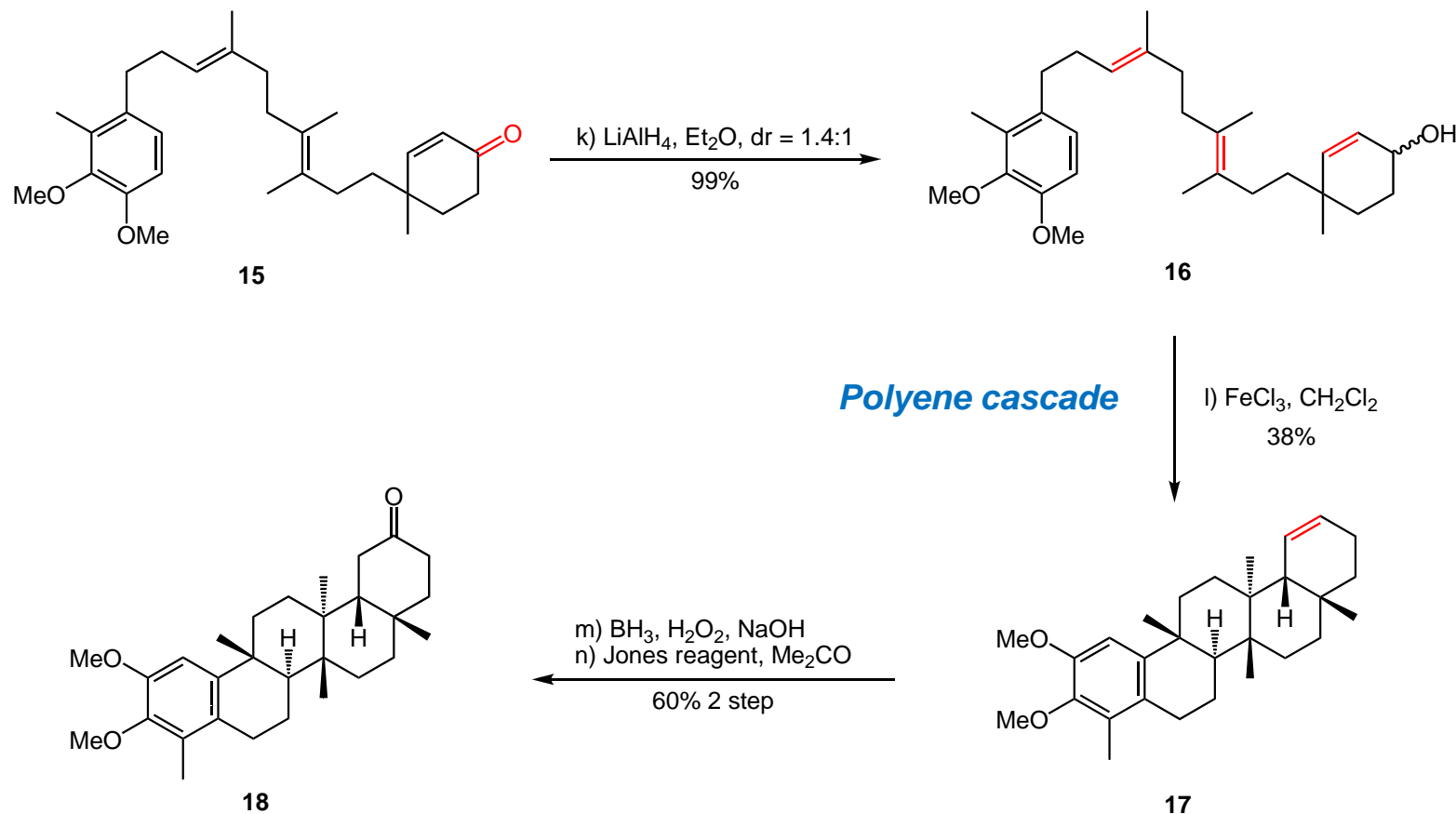
Siegel, D. *et al.* *J. Am. Chem. Soc.* **2015**, *137*, 11864.

Total Synthesis of Celastrol



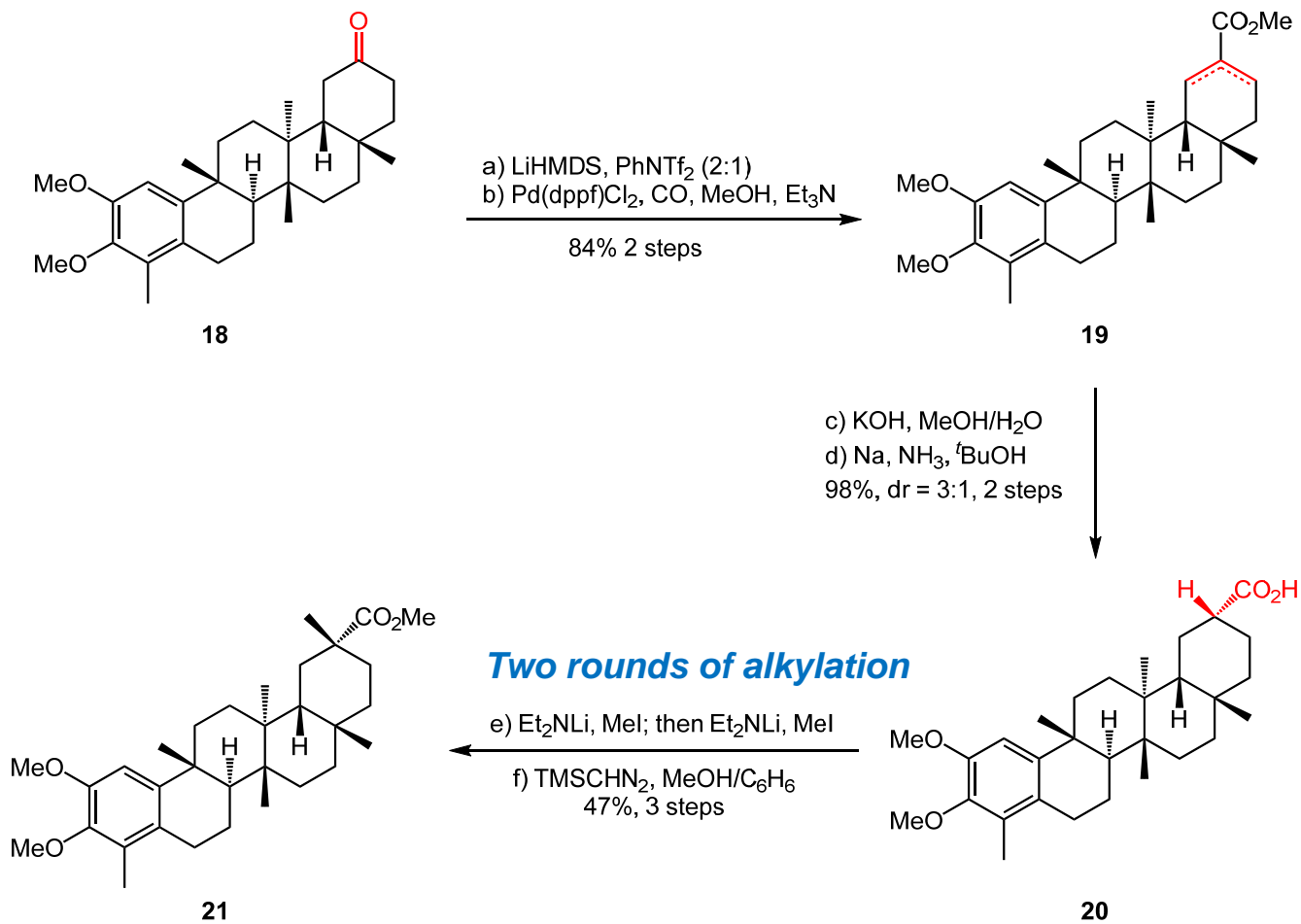
Siegel, D. *et al.* *J. Am. Chem. Soc.* **2015**, *137*, 11864.

Total Synthesis of Celastroid



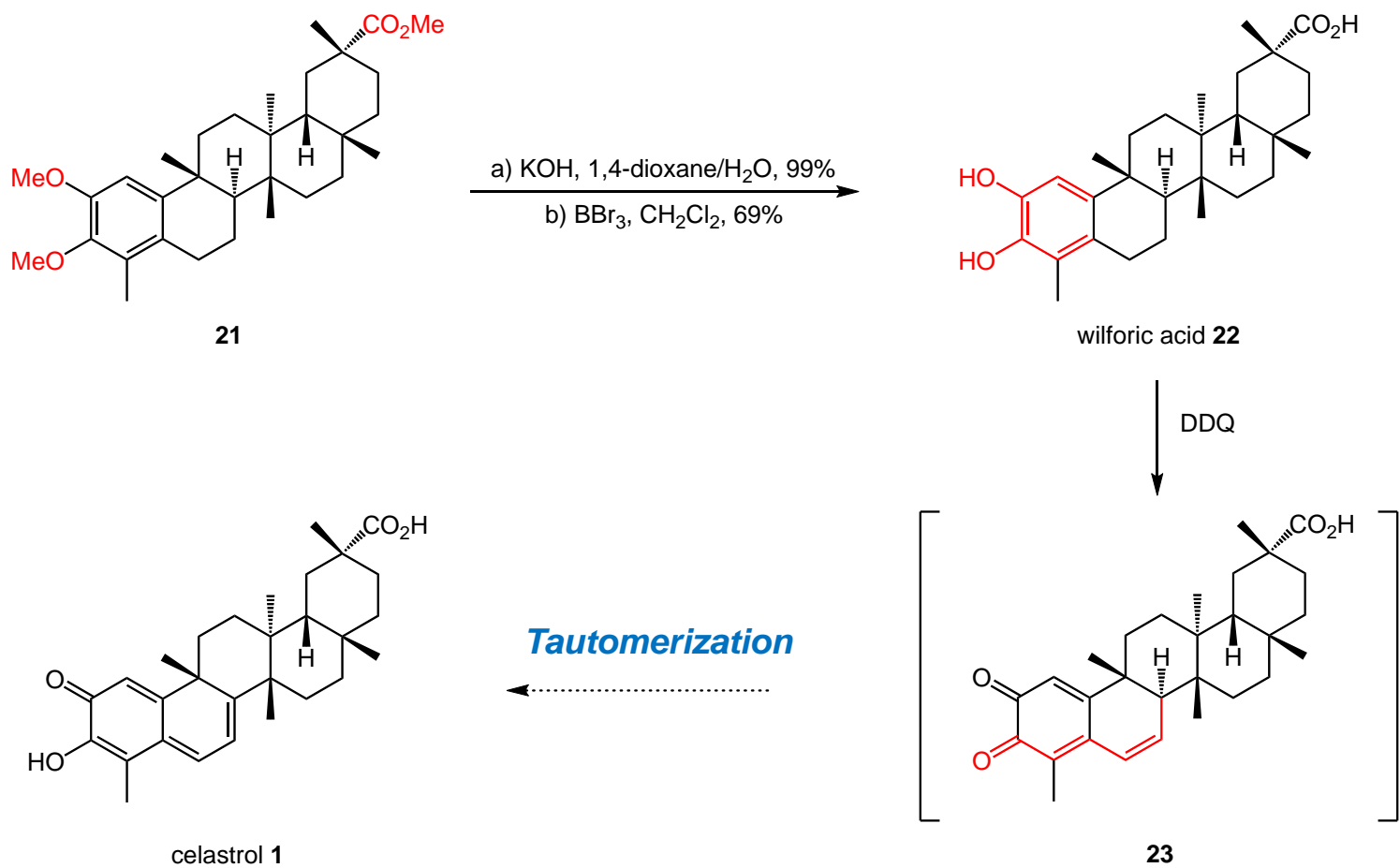
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Total Synthesis of Celastrol



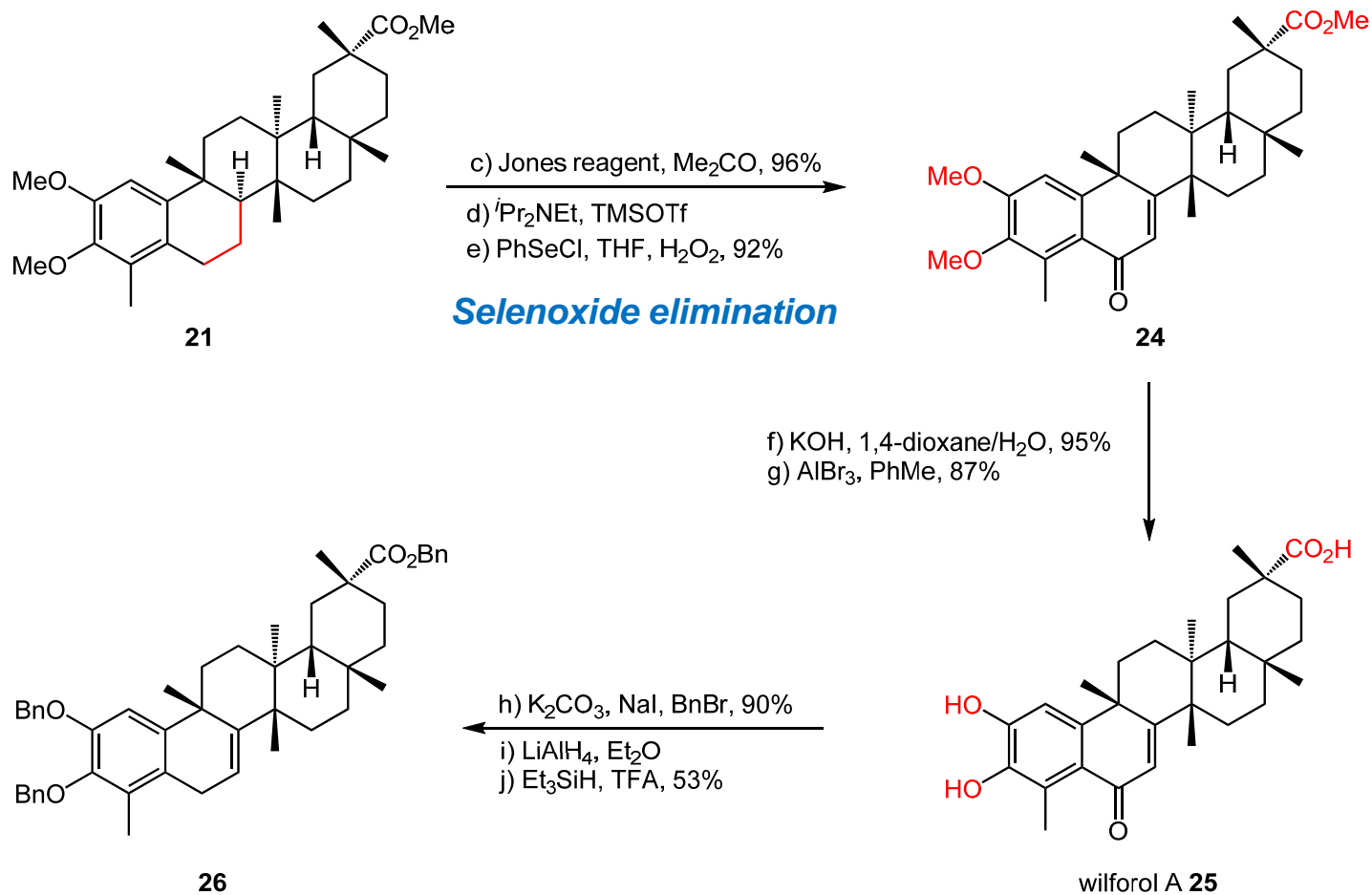
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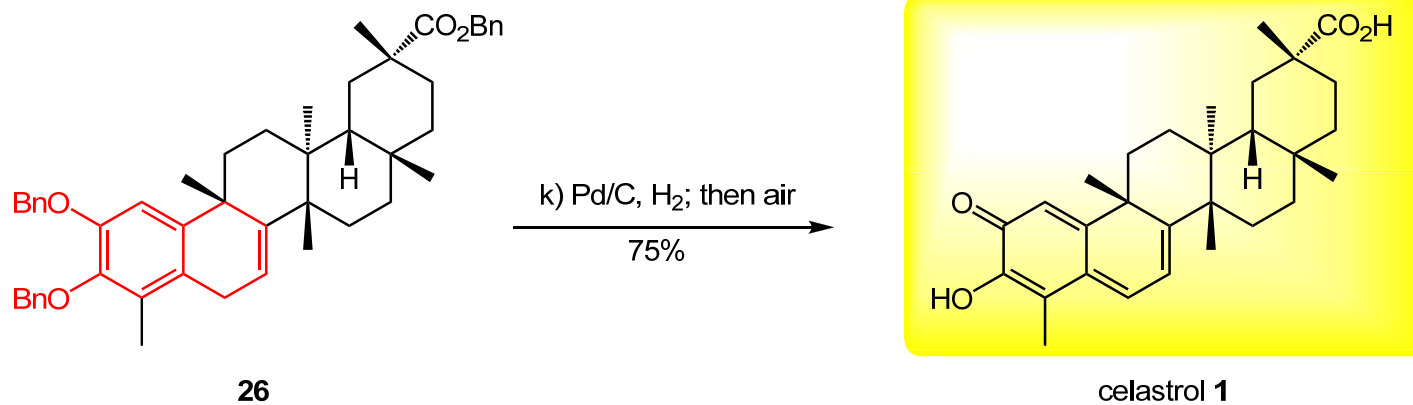
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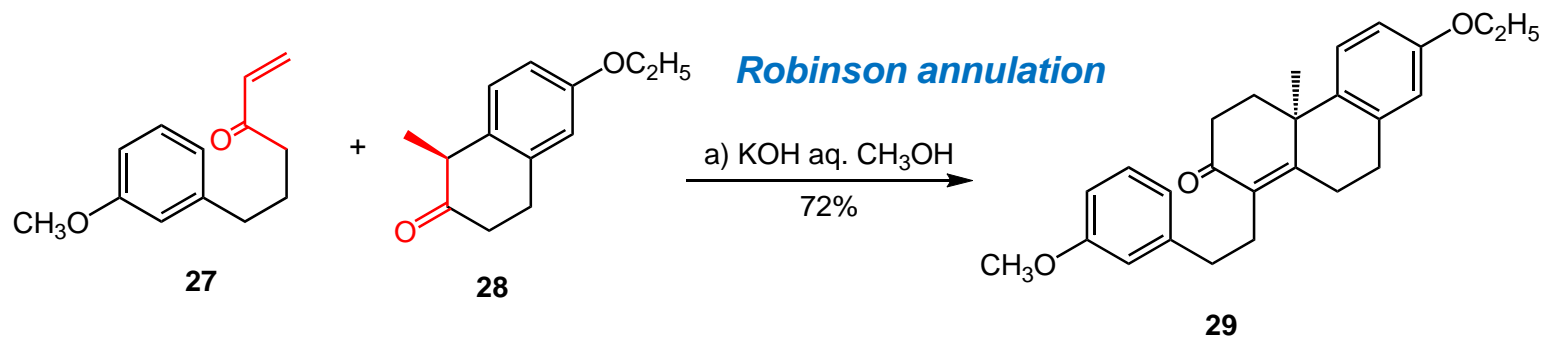
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Total Synthesis of Celastrol



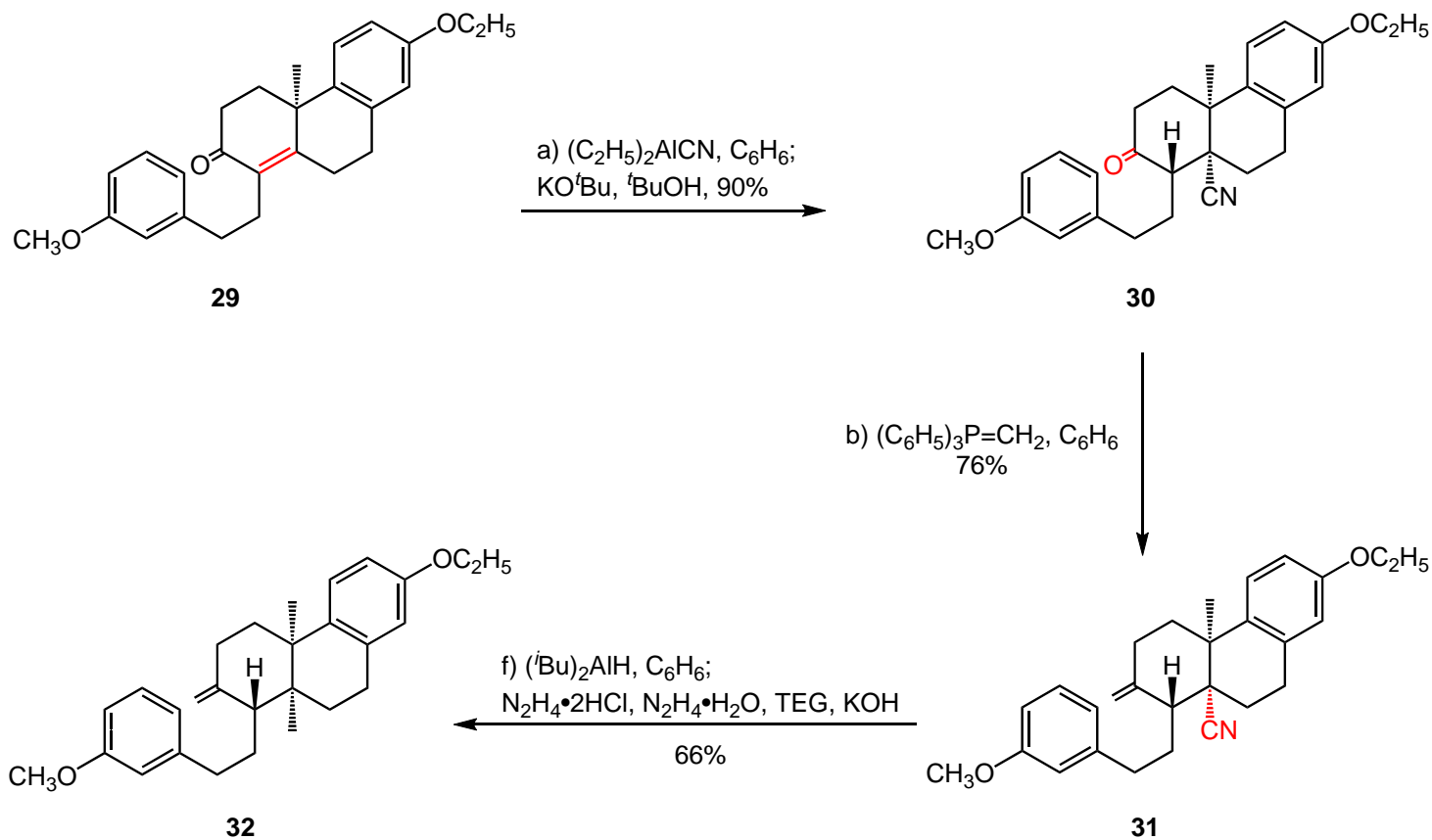
Siegel, D. *et al.* *J. Am. Chem. Soc.* **2015**, *137*, 11864.

Total Synthesis of *d*-Alnusenone



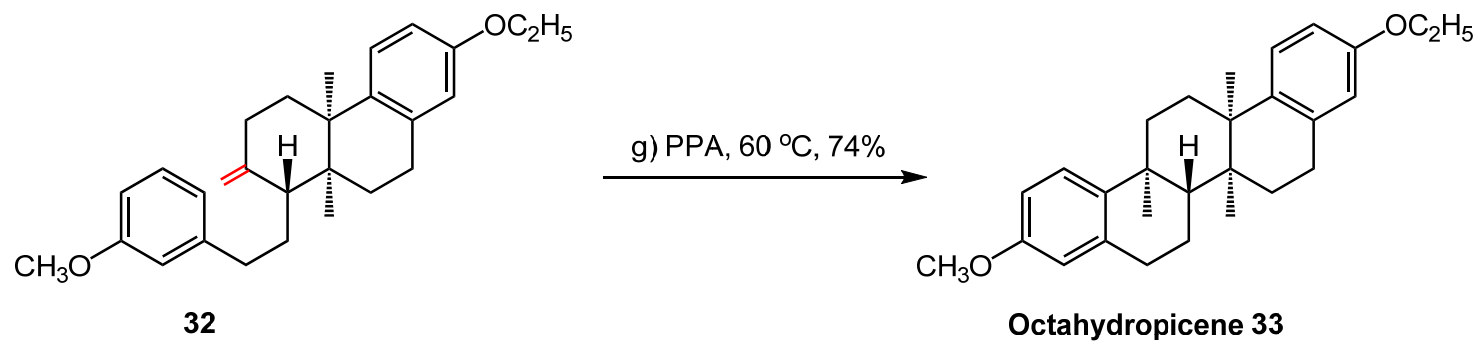
Ireland, R. E. *et al.* *J. Am. Chem. Soc.* **1973**, *95*, 7829.

Total Synthesis of Octahydropicenes 33, 37



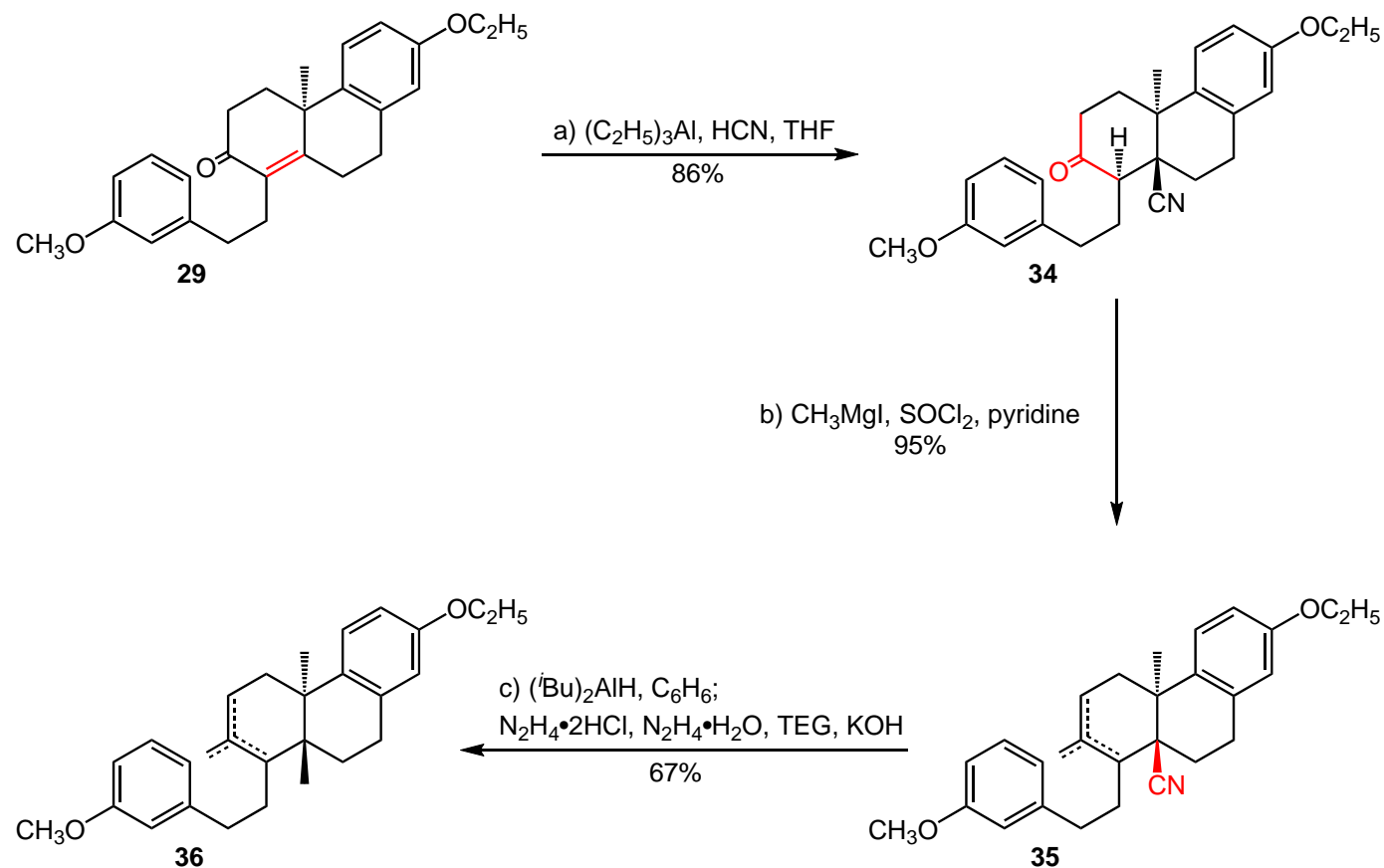
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Total Synthesis of Octahdropicenes 33, 37



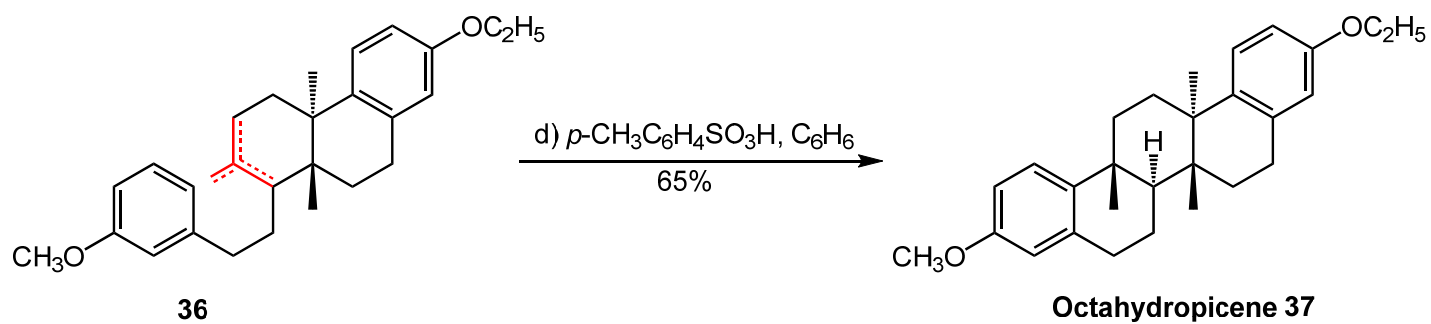
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Total Synthesis of Octahydropicenes 33, 37



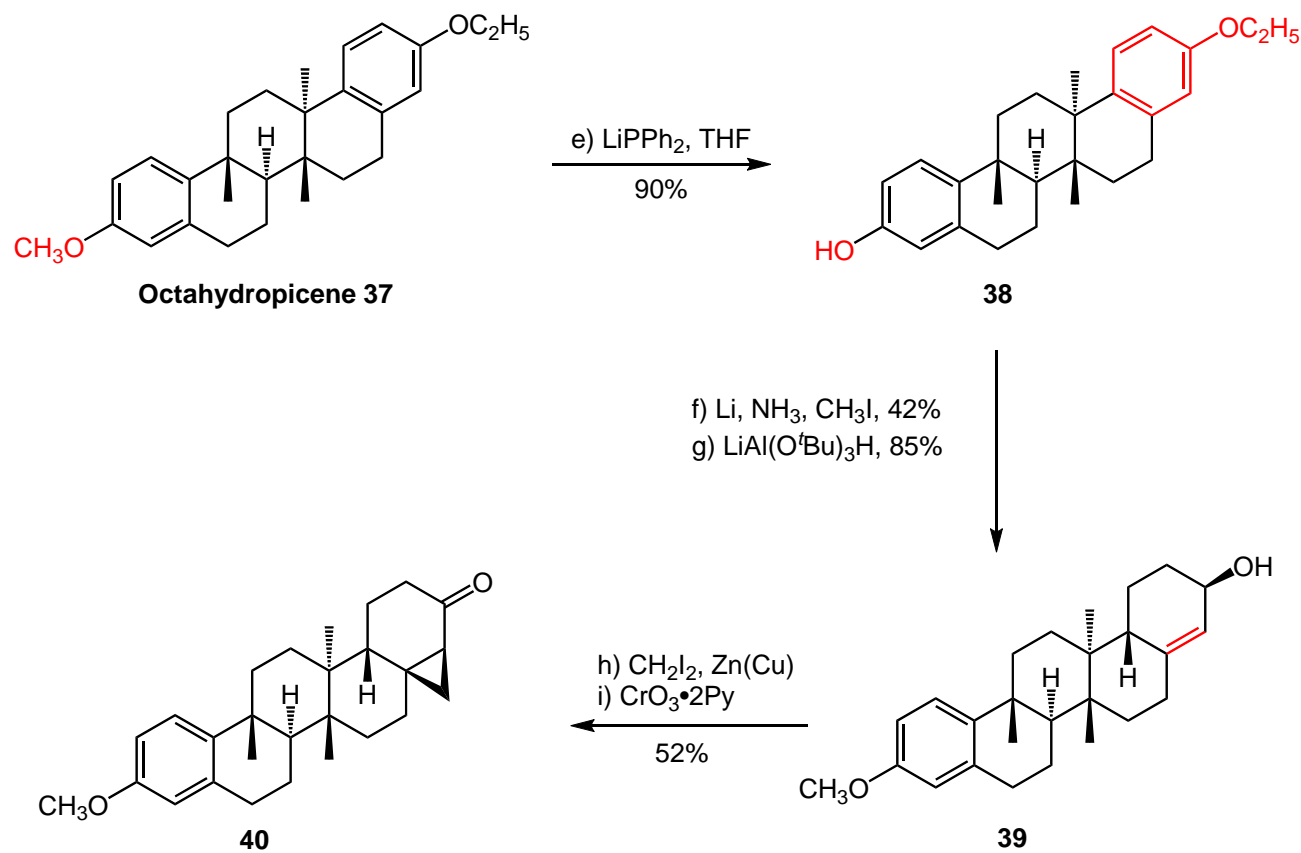
Ireland, R. E. *et al.* *J. Am. Chem. Soc.* **1973**, *95*, 7829.

Total Synthesis of Octahydronicenes 33, 37



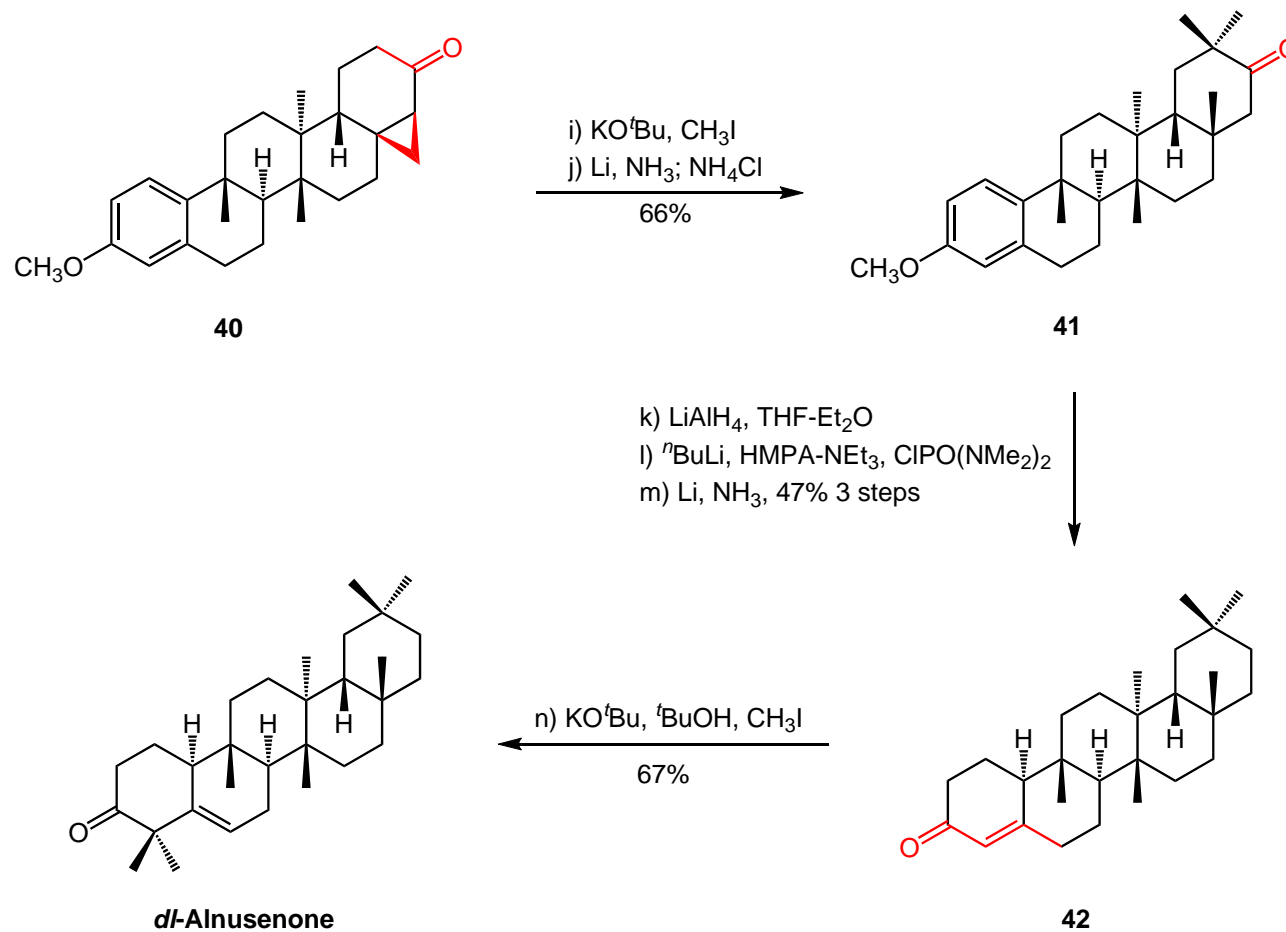
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Total Synthesis of *d*-Alnusenone



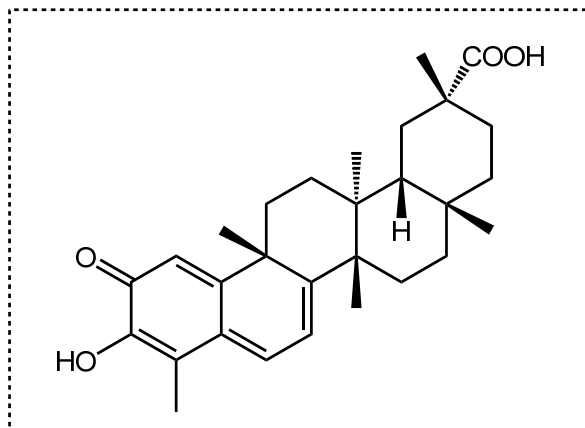
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Total Synthesis of *dl*-Alnusenone



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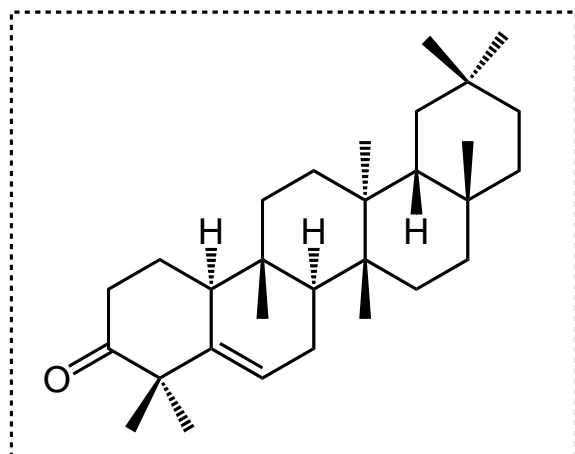
Summary



Celastrol

- ◆ Pentacyclic framework of the celastroid class
- ◆ FeCl₃-mediated polyene cascade
- ◆ 31 steps linear sequence, 0.5% yield
- ◆ Related : wilforic acid, wilforol A

Siegel, D. *et al. J. Am. Chem. Soc.* **2015**, *137*, 11864.



dl-Alnusenone

- ◆ Pentacyclic system of *dl*-alnusenone type
- ◆ Robinson annulation, Friedel-Crafts reaction
- ◆ 17 steps linear sequence, 0.9% yield

Ireland, R. E. *et al. J. Am. Chem. Soc.* **1973**, *95*, 7829.

Celastrol was initially isolated from *Tripterygium wilfordii* (thunder of god vine) and later identified in a variety of plant species in the Celastraceae family. **The natural product has a wide array of promising activities relevant to neuronal degeneration, inflammation, diseases caused by protein misfolding, cancer, and obesity.** The related celastroid natural product, tingenone, has been examined in clinical trials for skin, stomach, and lymphoepithelioma and shown to possess moderate activity with minimal side effects. **Medicinal chemistry optimization of the triterpene oleanolic acid arrived at CDDO methyl ester.** While not a member of the celastroid family, CDDO methyl ester is similarly related, as it possesses a strong Michael acceptor within a triterpene scaffold and continues to be used in multiple clinical trials.

In conclusion, a platform utilizing a polyene cascade was developed to provide access to the pentacyclic framework of the celastroid class of triterpenoids, leading to the total synthesis of celastrol and related natural products wilforic acid, and wilforol A. **The allylic alcohol cyclization precursor is accessed in >5 g quantities in 12 steps (longest linear) with an overall yield of 21%.** The developed cascade employs ferric chloride as an activator in a dilute solution of CH₂Cl₂ to generate the pentacycle in 38% yield on gram scale and showcases the utility of this reagent for polyene cyclizations. **Through this intermediate, the first syntheses of celastrol were completed in 31 and 32 (longest linear steps, respectively) as well as wilforic acid and wilforol A.**