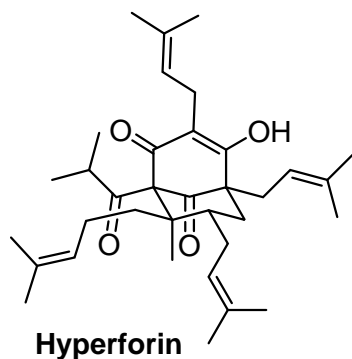


## Enantioselective Total Synthesis of Hyperforin

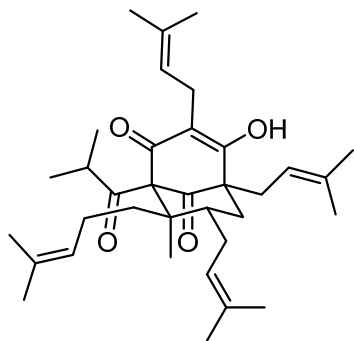
Brian A. Sparling, David C. Moebius, and Matthew D. Shair\*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

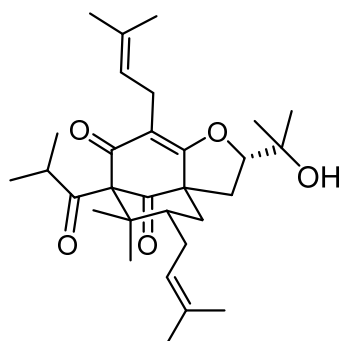


Benjamin R. Eyer  
Wipf Group-Current Literature  
January 12, 2013

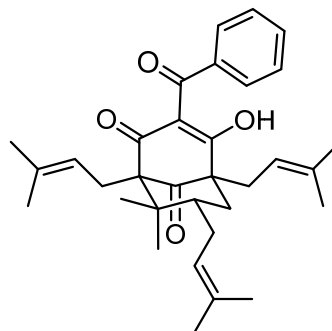
# Polycyclic Polyprenylated Acylphloroglucinol (PPAP) Natural Products



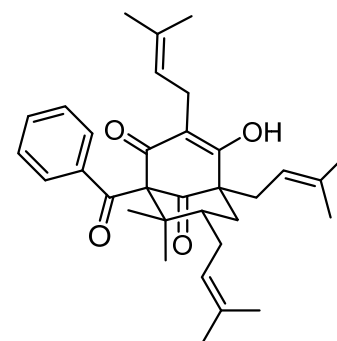
Hyperforin



Garsubellin A

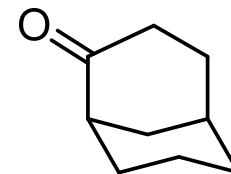


Clusianone

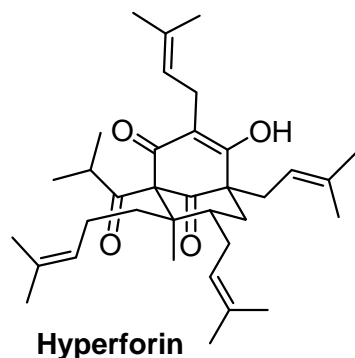


Nemorosone

- Bicyclo[3.3.1]nonanone core
  - Highly oxygenated
  - Dense prenyl and/or geranyl side chain substitution
- Biological activity
  - Antimicrobial
  - Antidepressant
  - Antioxidant
  - Cytotoxic
  - Anti-HIV



# Isolation and Structural Confirmation



- First isolated in 1971 from St. John's Wort (*Hypericum perforatum*)
- Characterized by NMR and X-ray
- Relative and absolute stereochemistry determined by an X-ray crystal structure of the 3,5-dinitrobenzoate ester

*Antibiotiki* **1971**, 16, 510.

*Tetrahedron Lett.* **1975**, 16, 2791.

*Tetrahedron Lett.* **1982**, 23, 1299.

*Acta Chem. Scand. A* **1983**, 37, 263.

# Biological Activity and Stability

- Constituent of St. John's Wort responsible for antidepressant activities
  - Blocks reuptake of neurotransmitters
  - Possible MOA: selective activation of TRPC6 (classical transient receptor potential protein)
  - Possible treatment of depression and other diseases
- Therapeutic potential limited
  - Poor water solubility
  - Facile oxidation when exposed to light and air
  - Potent activation of pregnane X receptor
  - Limited ability to manipulate isolated material (semisynthetic analogs)



St. John's Wort 300 mg Standardized Extract, 100 Capsules

[Vitamin World](#) > [Shop By Categories](#) > [St John's Wort](#)

★★★★★ [Write the first review](#)



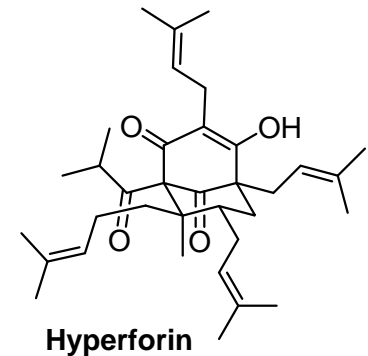
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## Biological Activity:

*Psychopharmacology* **2001**, 153, 402.  
*Trends Pharmacol. Sci.* **2001**, 22, 292.  
*Pharmacol. Res.* **2003**, 47, 101.  
*Komplementmed.* **2009**, 16, 146.  
*Life Sci.* **1998**, 63, 499.  
*FASEB J.* **2007**, 21, 4101.

## Stability:

*Phytochemistry* **1998**, 49, 1305.  
*Phytochem. Anal.* **2003**, 14, 290.  
*Eur. J. Org. Chem.* **2004**, 1193.  
*J. Agric. Food Chem.* **2004**, 52, 6156.  
*Lett. Org. Chem.* **2008**, 5, 583.

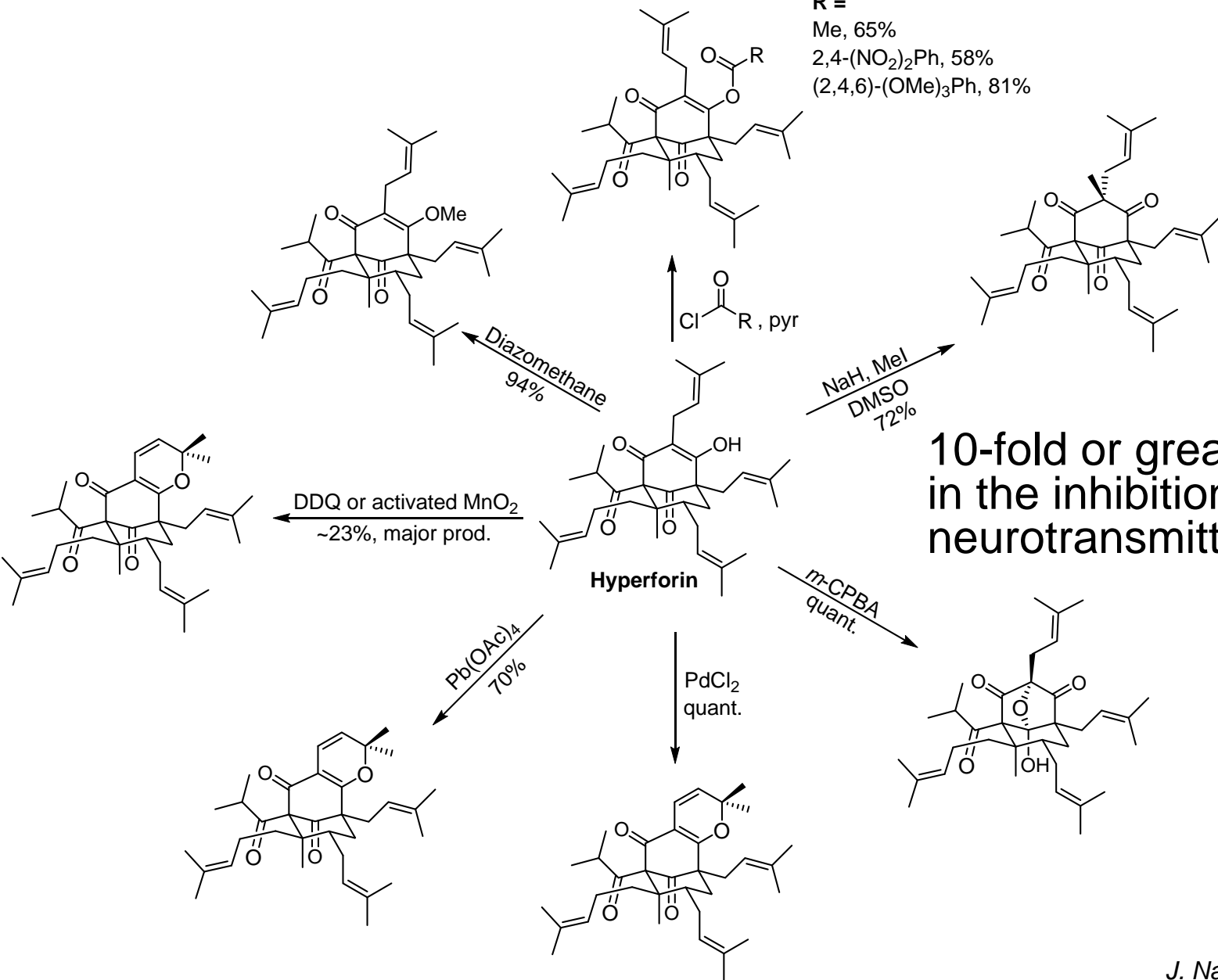
# Structural Modification of Hyperforin

R =

Me, 65%

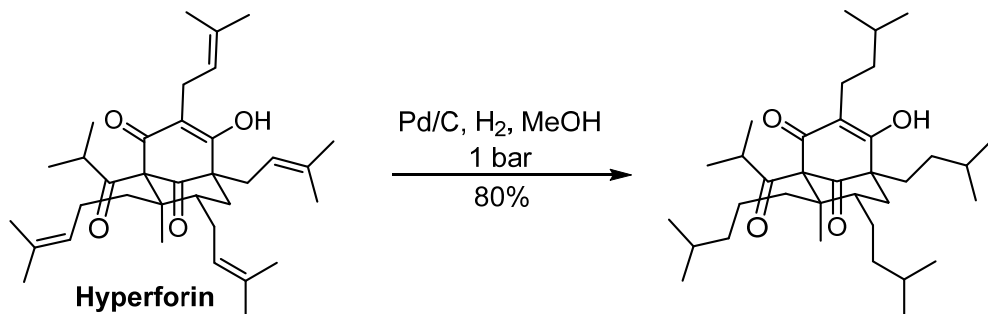
2,4-(NO<sub>2</sub>)<sub>2</sub>Ph, 58%

(2,4,6)-(OMe)<sub>3</sub>Ph, 81%

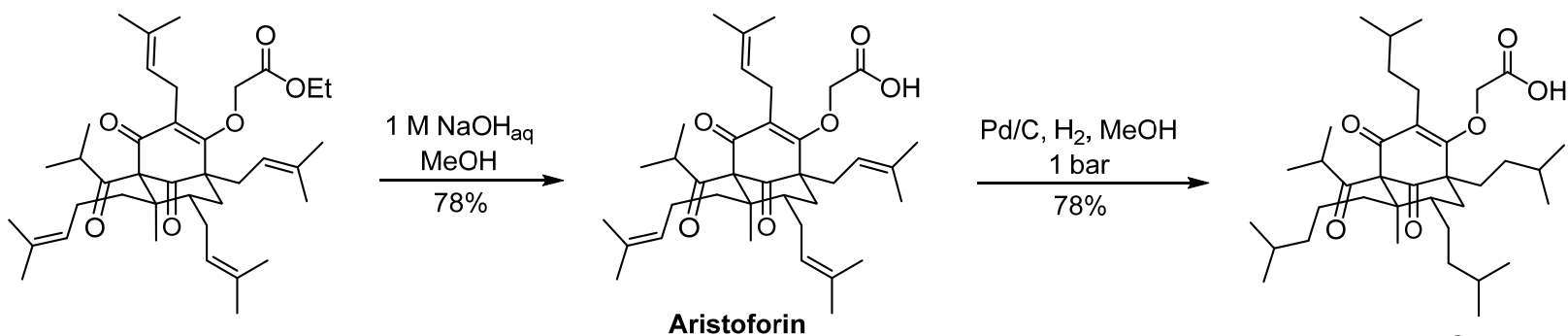
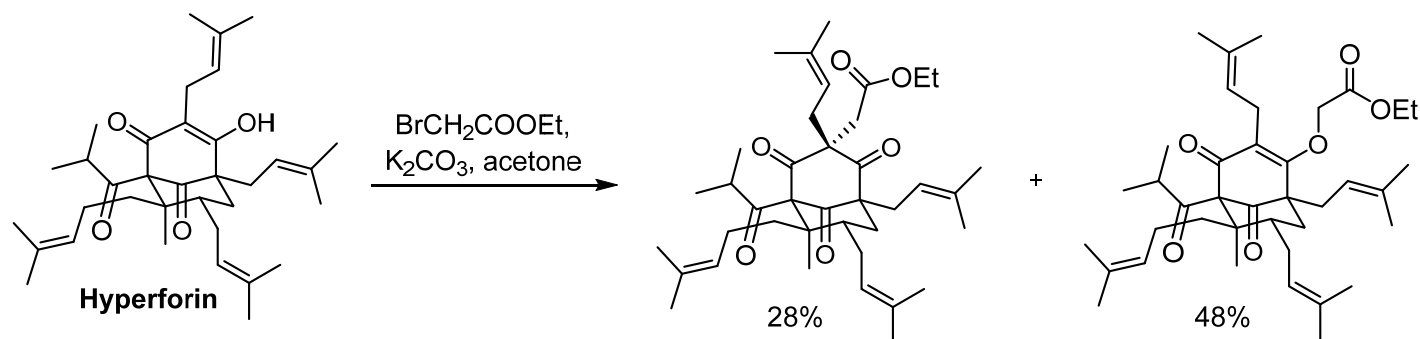


10-fold or greater decrease  
in the inhibition of  
neurotransmitter reuptake

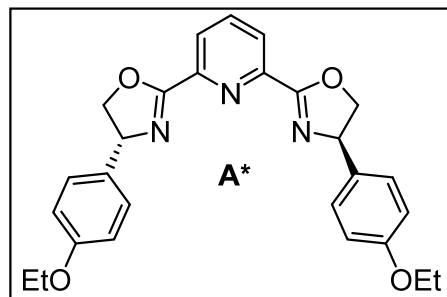
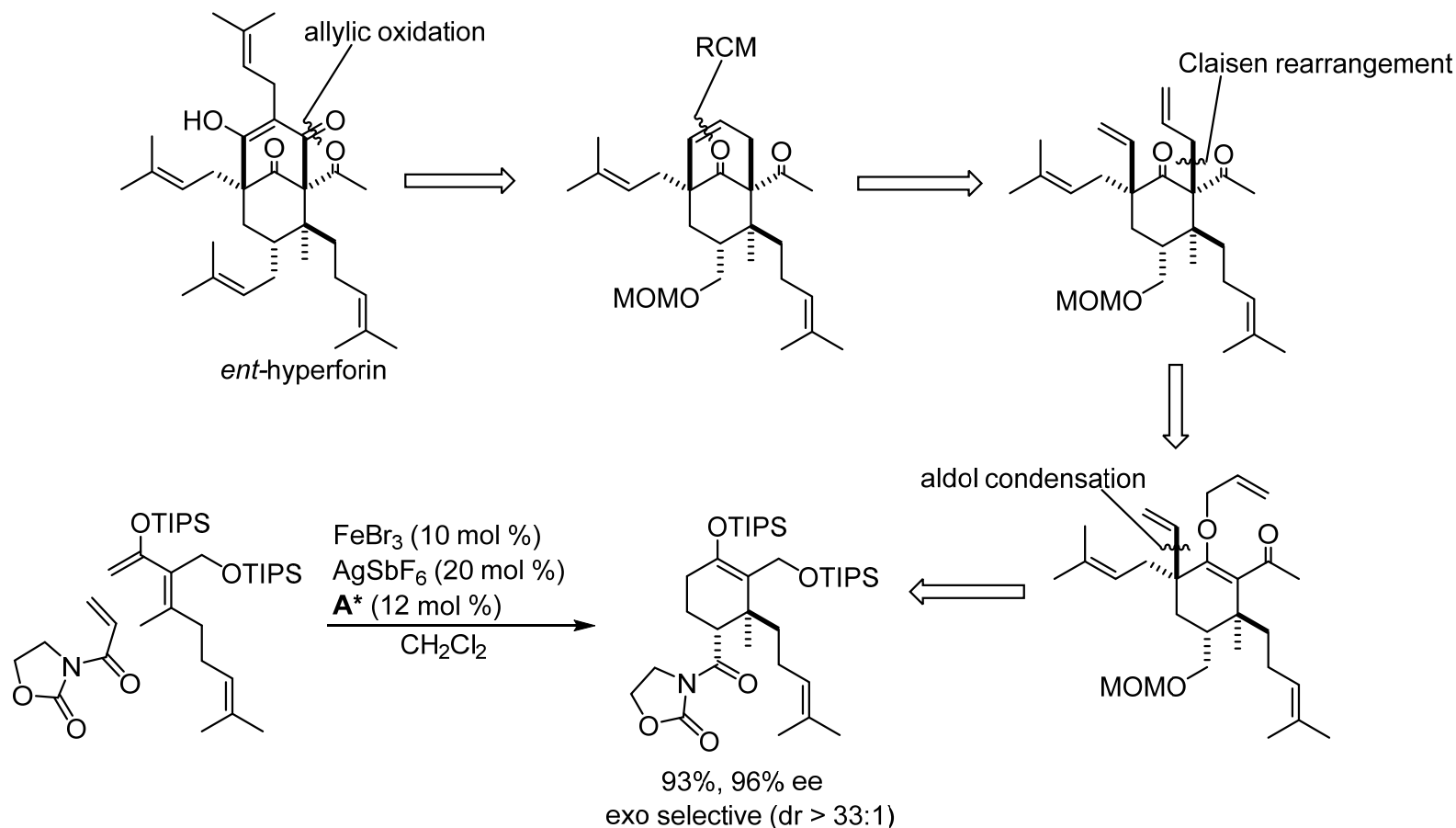
# Structural Modification of Hyperforin Cont.



- Increased solubility
- Stable in solution for a week (DMSO and  $\text{H}_2\text{O}$ )
- Aristoforin: anti-tumor activity *in-vitro* and *in-vivo*

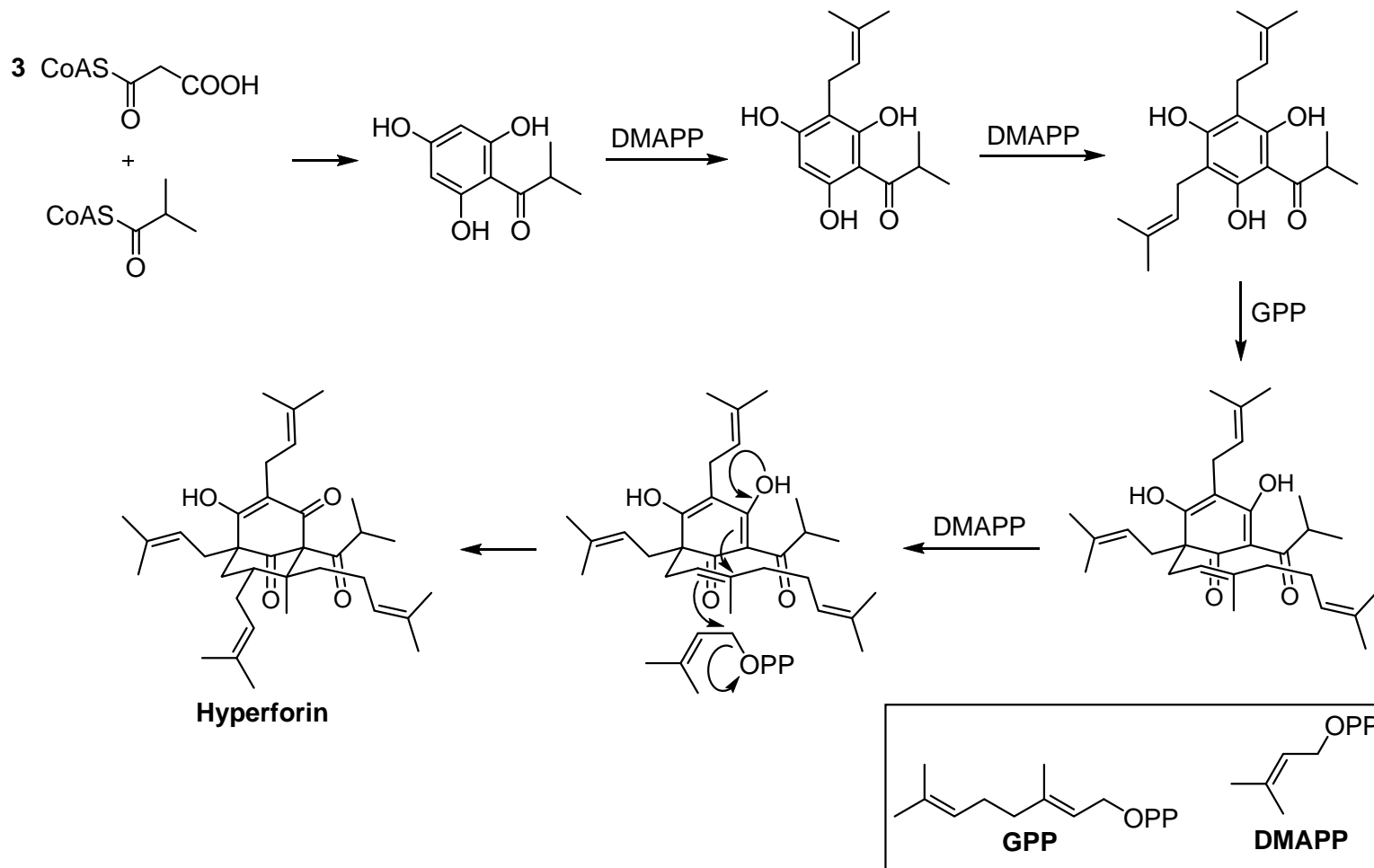


# Synthesis of *ent*-hyperforin



51 steps from propargyl bromide!!!

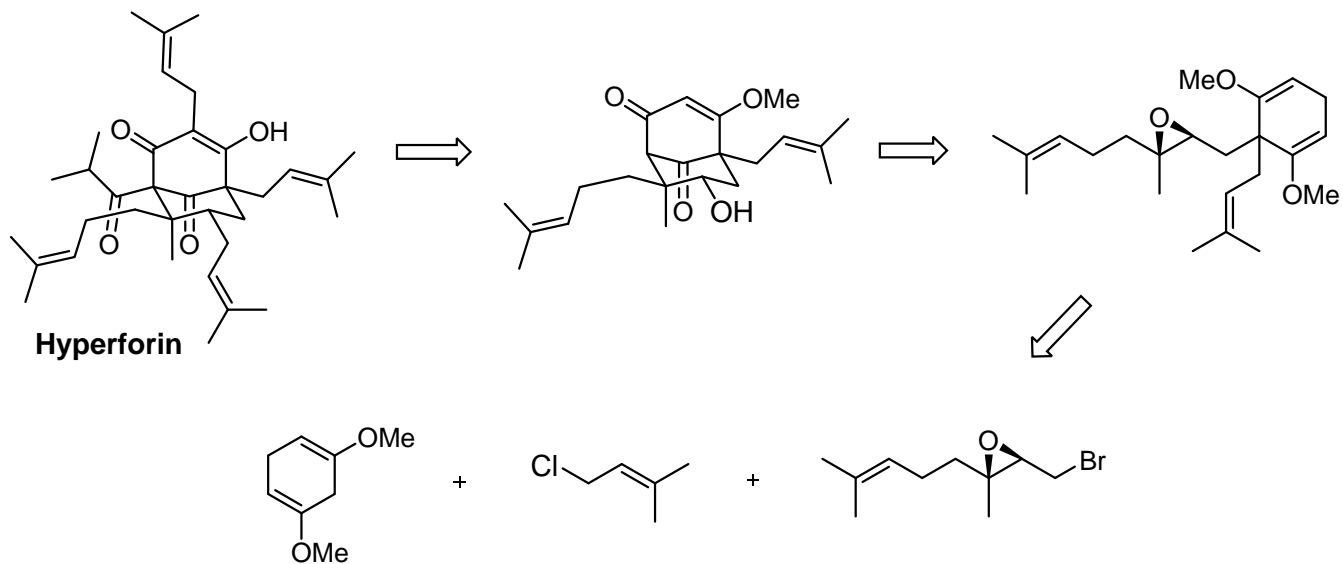
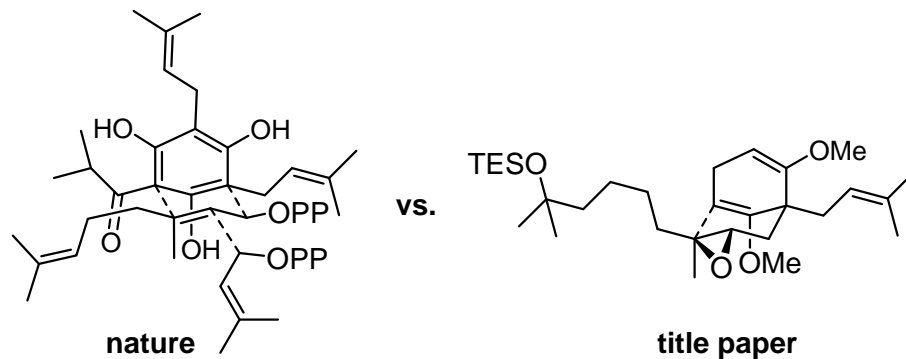
# Bio-synthesis



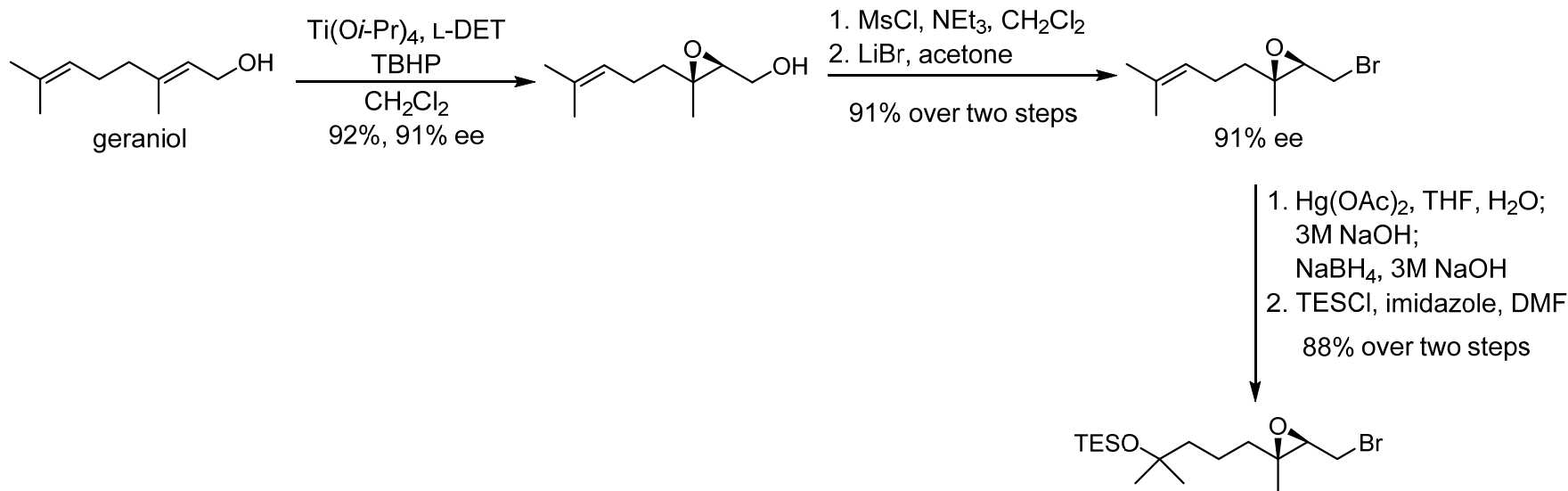
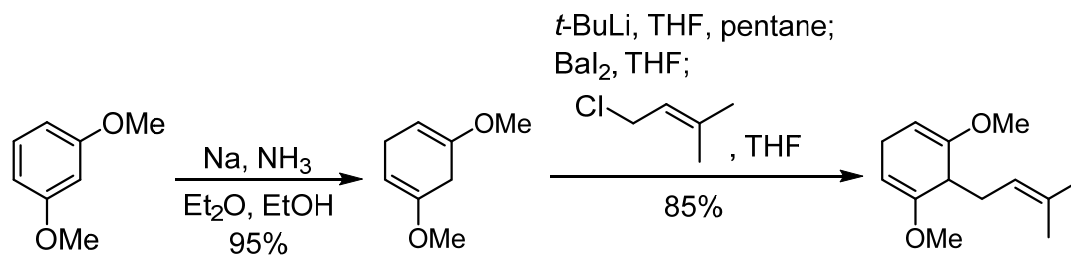
*J. Med. Chem.* **2002**, 45, 4786.  
*Phytochemistry* **2005**, 66, 51.  
*Phytochemistry* **2005**, 66, 139.  
*Phytochemistry* **2007**, 68, 1038.



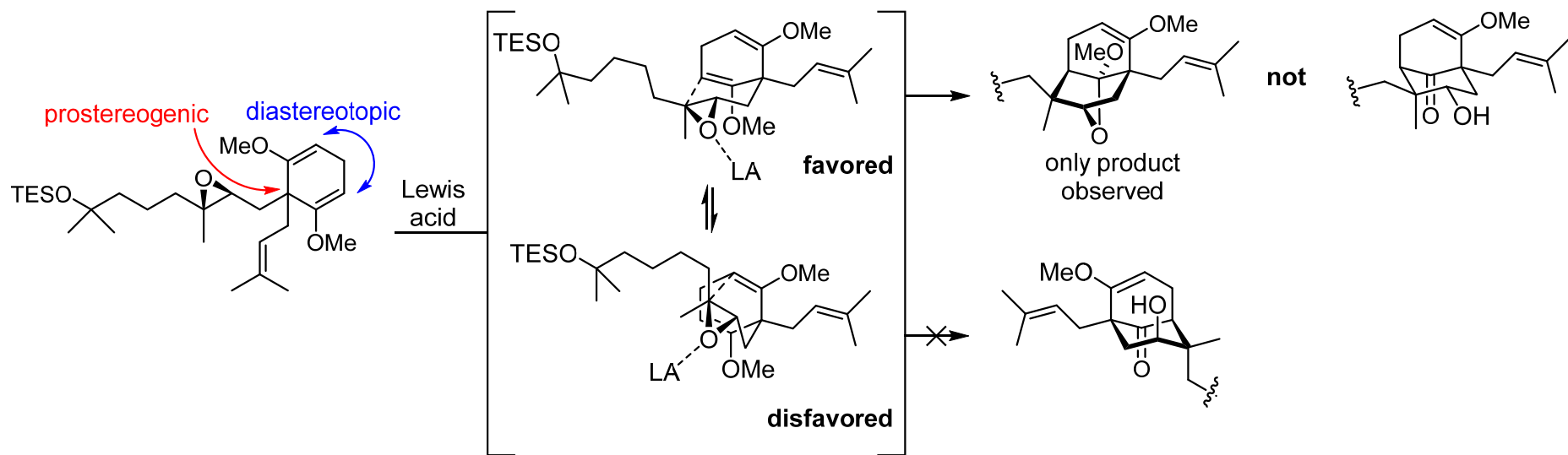
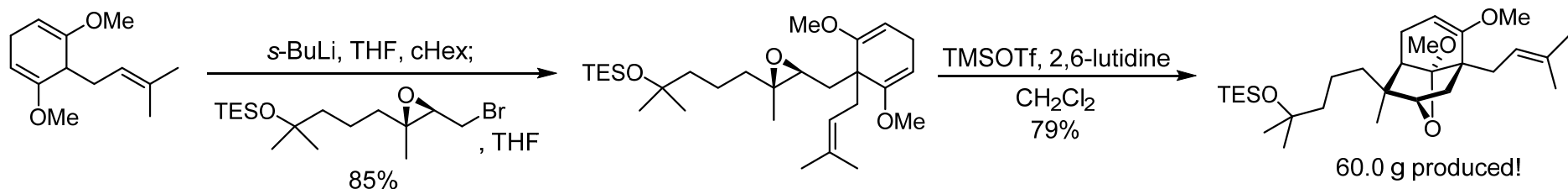
# Title Paper: Retrosynthetic analysis



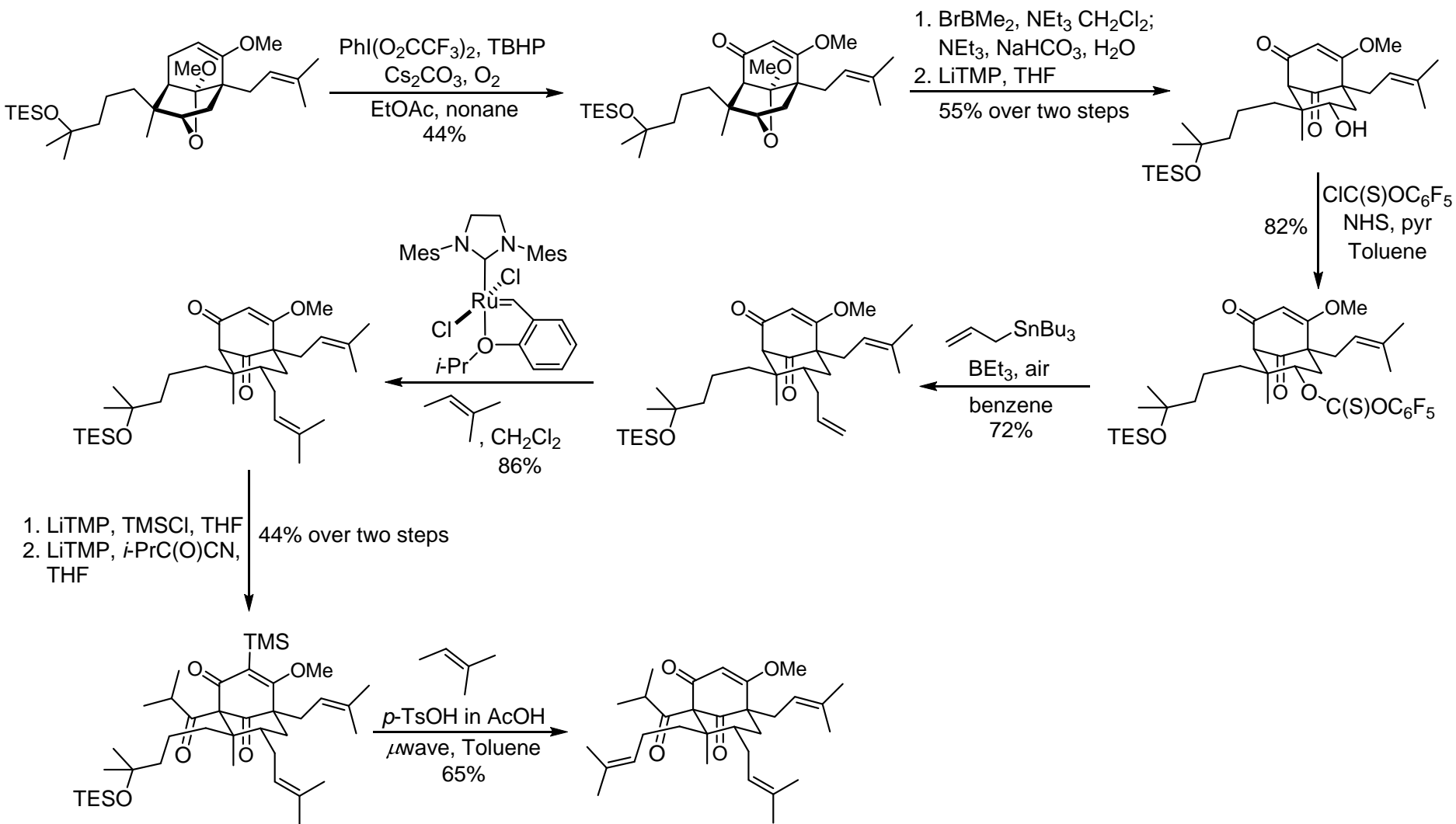
# Title Paper: Synthesis of Coupling Partners



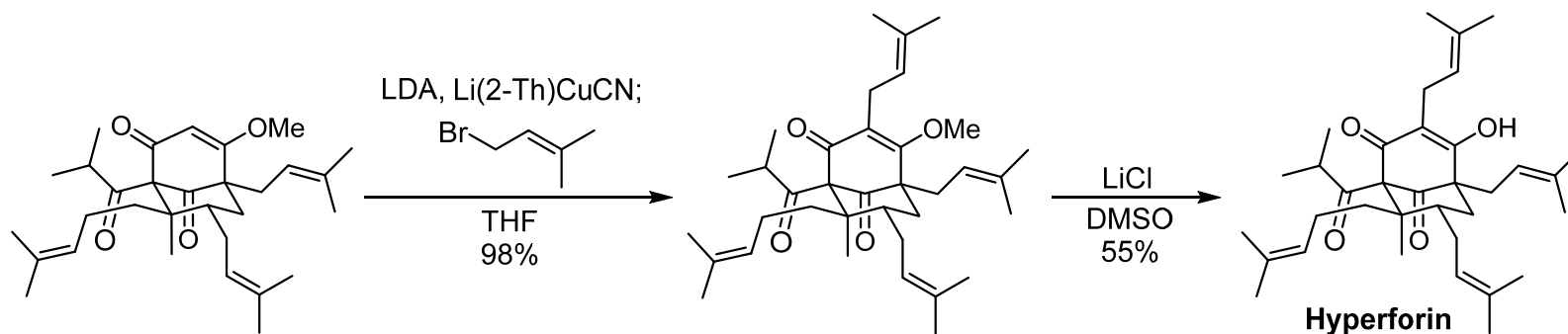
# Title Paper: Synthesis of Bicyclic Core



# Title Paper: Functionalization of the Core



# Title Paper: Completion of the Synthesis



- Enantioselective total synthesis
  - 18 steps longest linear sequence from geraniol
  - Highly scalable: 40 mg of Hyperforin prepared at publication
  - Key step: Latent symmetry elements to set two quaternary stereocenters and access the bicyclic core
- Modular route
  - Diverse analog synthesis *in-progress*
  - New analogs will be tested to probe mechanism(s) of bioactivity