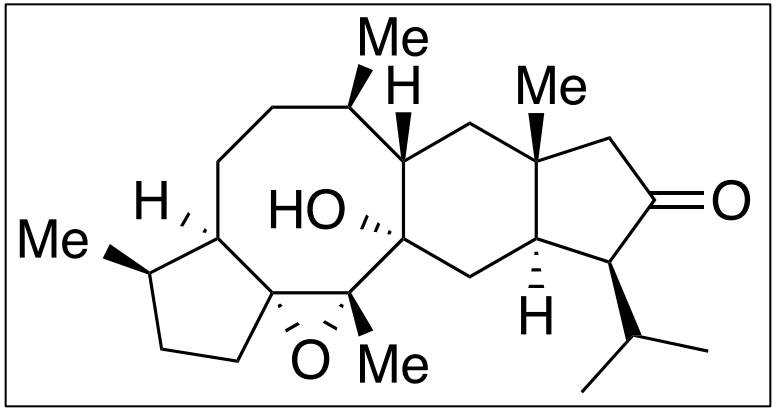
The Total Synthesis of (–)-Nitidasin



D. T. Hog, F. M. E. Huber, P. Mayer, D. Trauner,
Angew. Chem. Int. Ed. **2014**, *53*, 8513–8517

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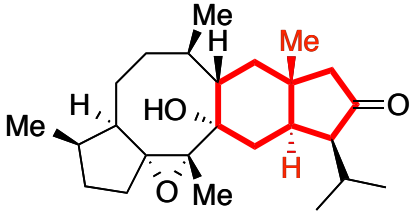
DOI: 10.1002/anie.201403605

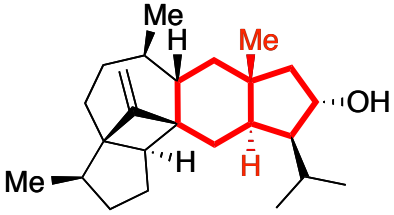
Samuel Rieder, 2. Oct. 2014

History
Isolation and Characterisation

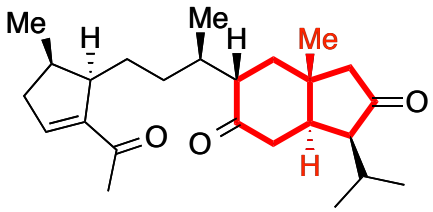
- Isolated from *Gentianella nitida* and *Gentianella alborosea*
- Used in Peruvian herbal infusions “Hercampuri“
- Remedy against hepatitis, diabetes and hypertension
- Sesterterpenoid (25 C), 5-8-6-5 skeleton, ten stereogenic centeres
- Oxygenated *trans*-hydrindane moiety



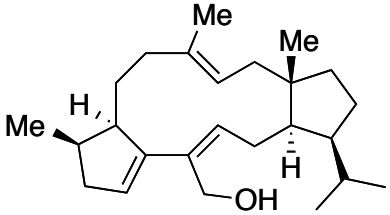
nitidasin



astellatol

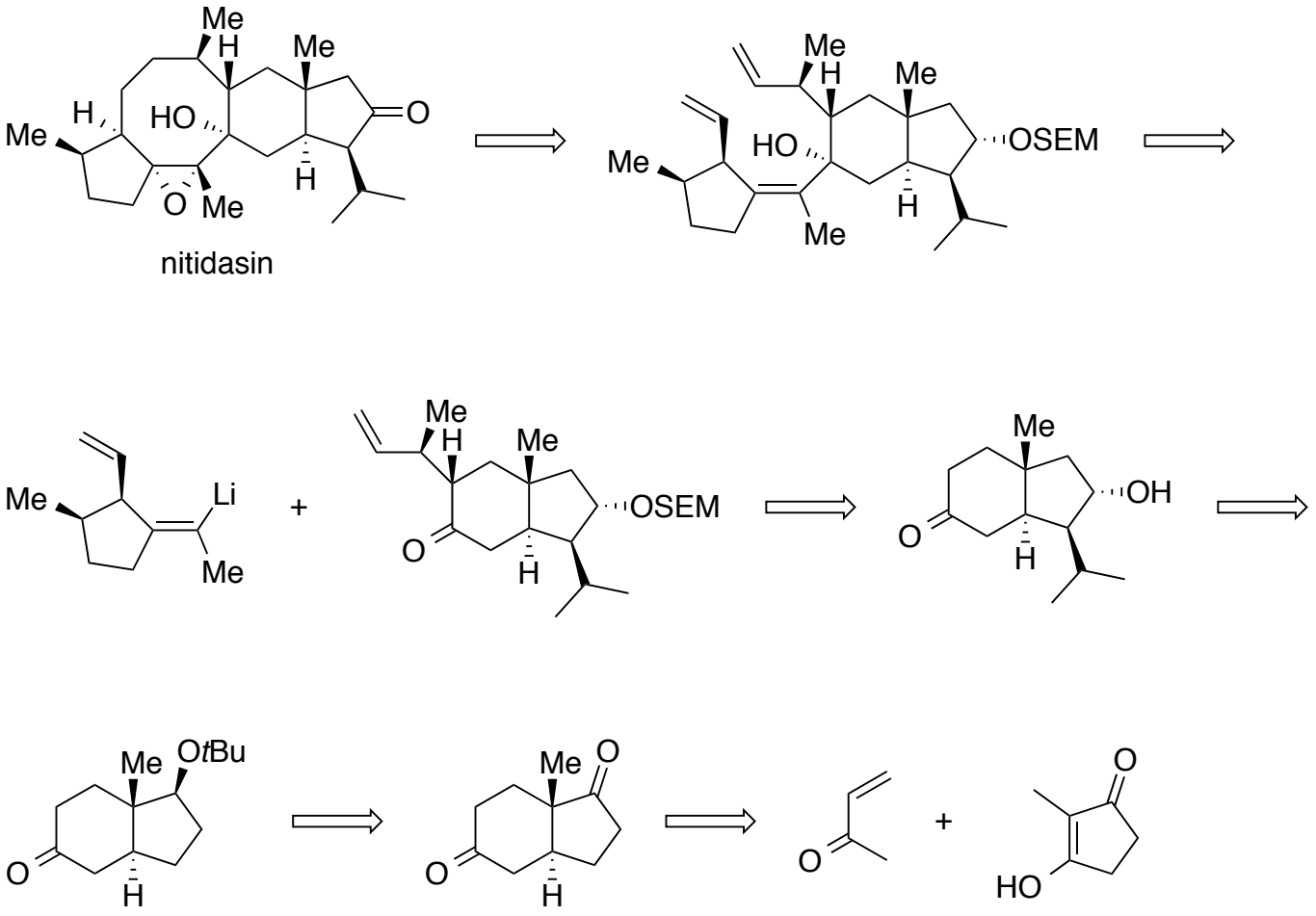


alborosin



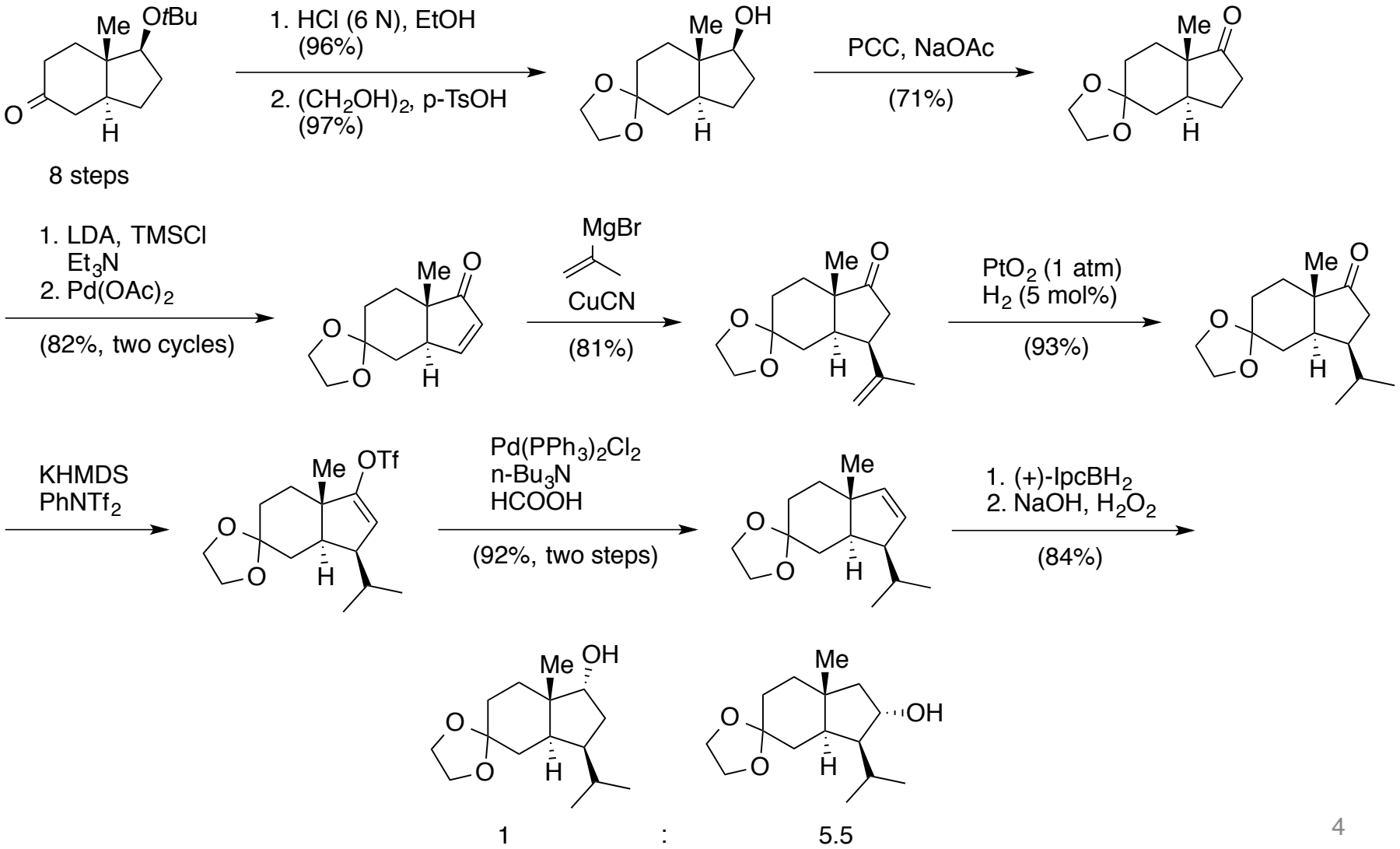
nitiol

Retrosynthesis



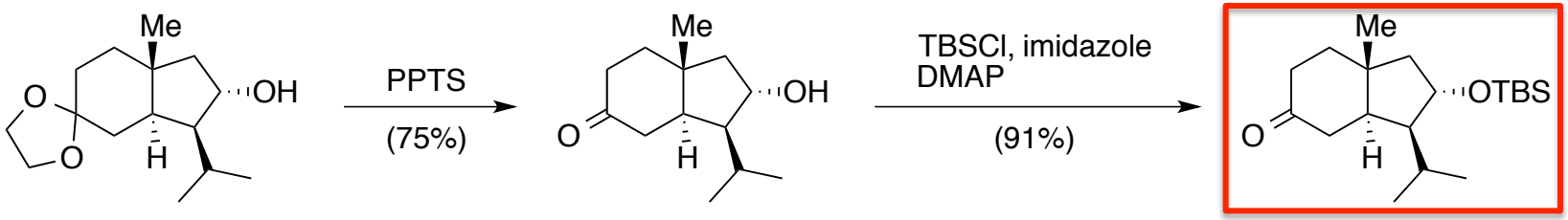
D. T. Hog, P. Mayer, D. Trauner, *J. Org. Chem*. **2012**, *77*, 5838–5843
Z. G. Hajos, D. R. Parrish, *Org. Synth*. **1985**, *63*, 26–31

Synthesis I
Preparation of Starting *trans*-Hydrindane

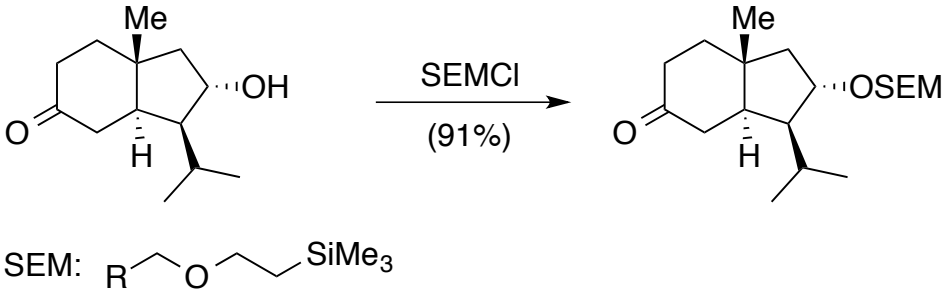


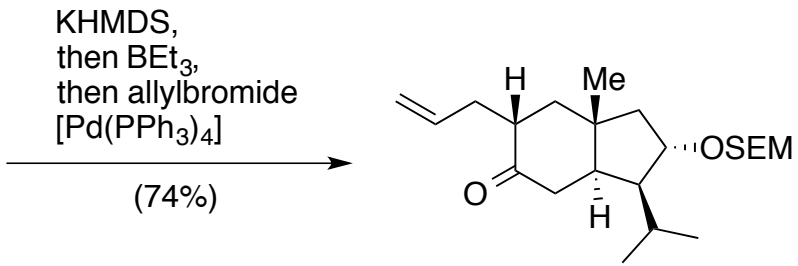
Synthesis II

Preparation of Starting *trans*-Hydrindane, First Building Block



- Possible to synthesize gram quantities of key ketone

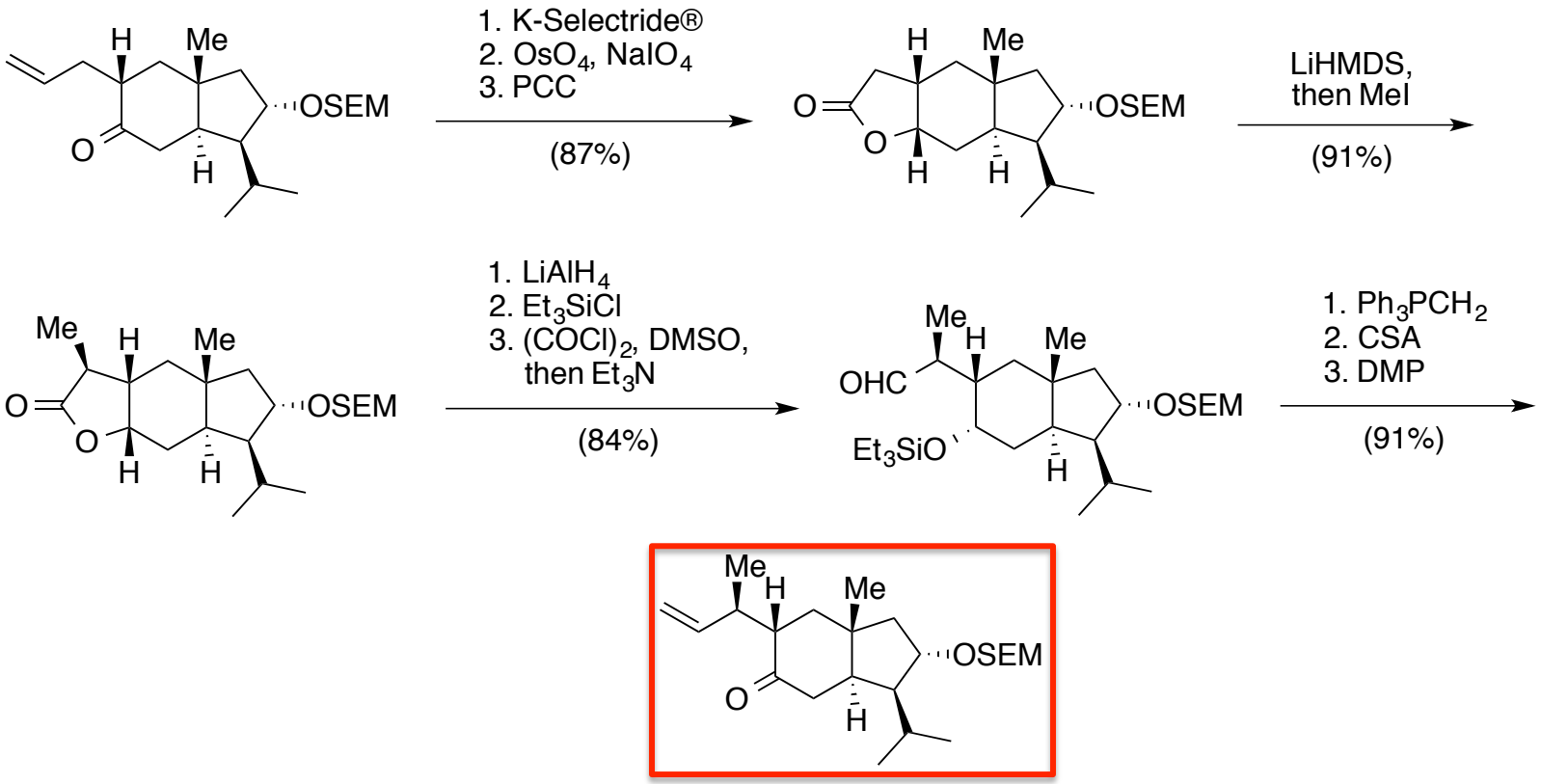




- Alkylation protocol developed by **Negishi**
- Other attempts with **standard alkylation** procedures were **unsuccessful**

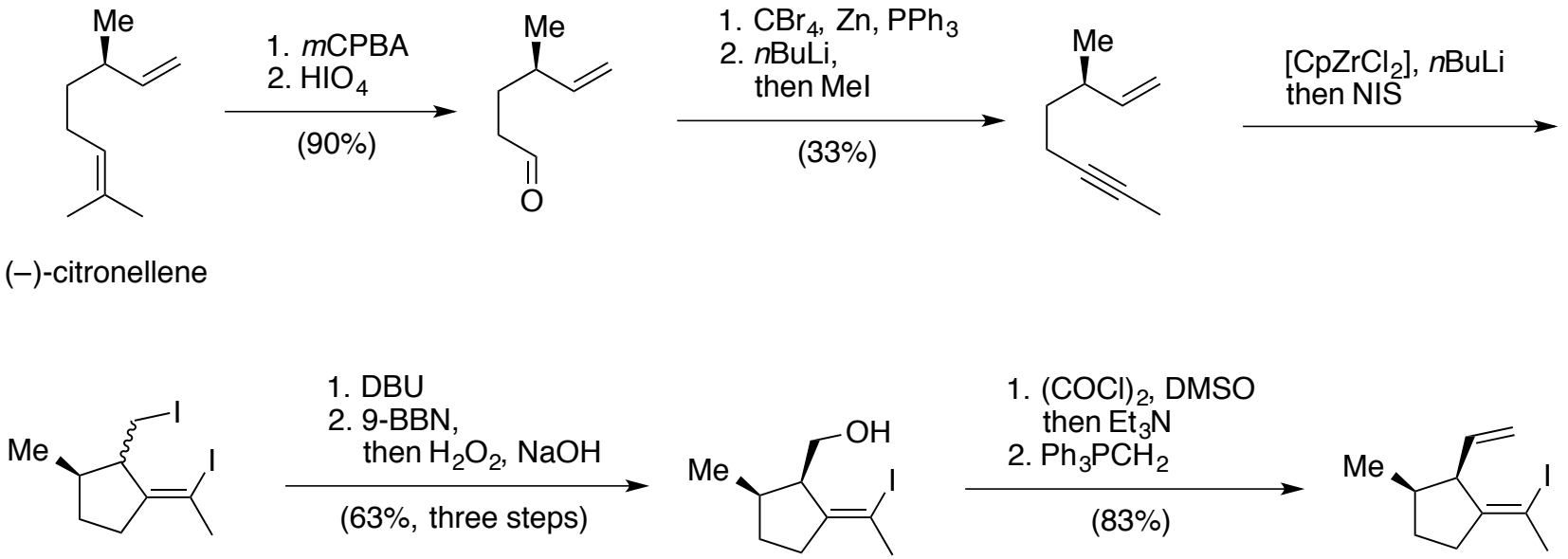
E.-I. Negishi, H. Matsushita, S. Chatterjee, R. A. John, *J. Org. Chem.* **1982**, *47*, 3188–3190

Synthesis III
First Building Block



- **Methylation** with MeI from the convex face → single diastereoisomer
- Double Silylation → **Chemoselective** Oxidation (carefully optimised conditions)
- Resulting ketone bearing **5 of 10 stereocenters** of nitidasin

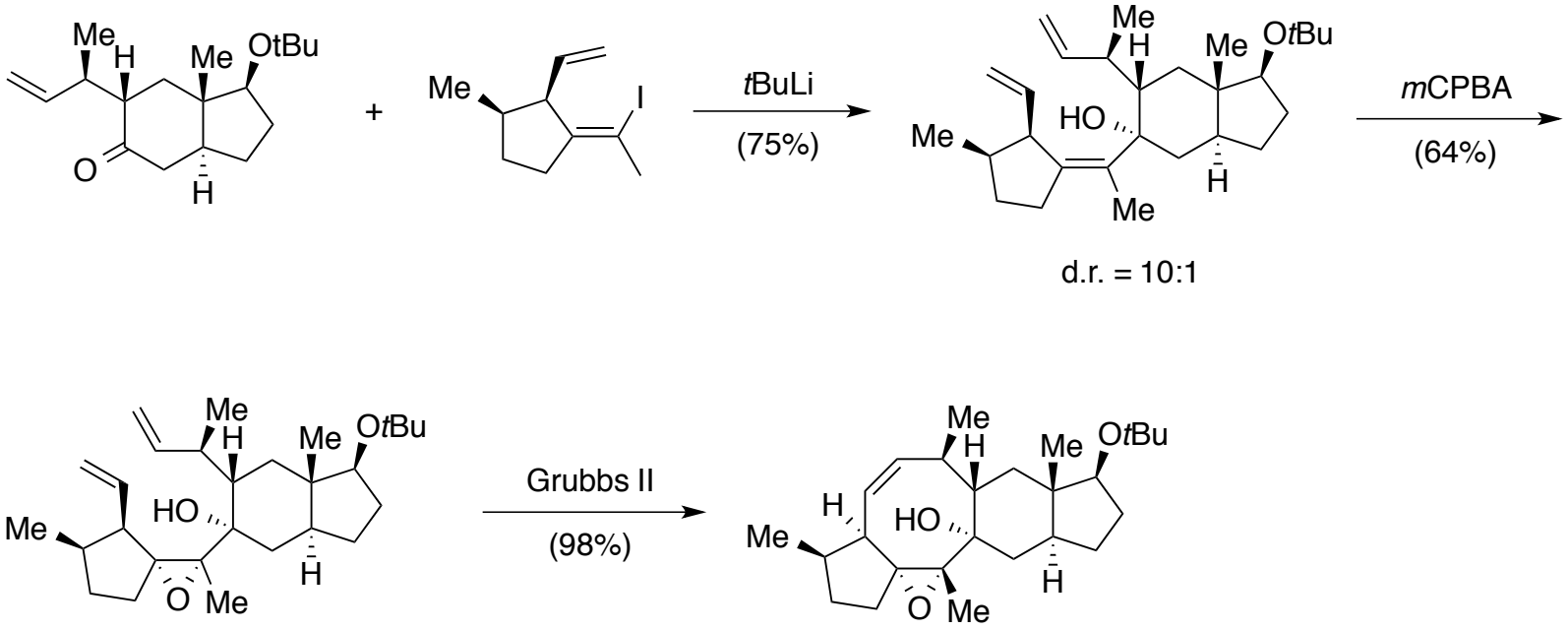
Synthesis IV
Second Building Block, Vinyl Lithium Precursor



- Corey-Fuchs Homolgation
- Zr-mediated **cyclometalation** by Negishi → *in situ* generation of Cp_2Zr
- Analysis using **Mosher's ester** (60% ee) → low optical purity of sm
- **Epimerisation** at the aldehyde stage **not** observed (allylic strain of an intermediary enolate

G. Angel, Z. Owczarczyk, E.-I. Negishi, *Tetrahedron Lett*. **1992**, *33*, 1543–1546

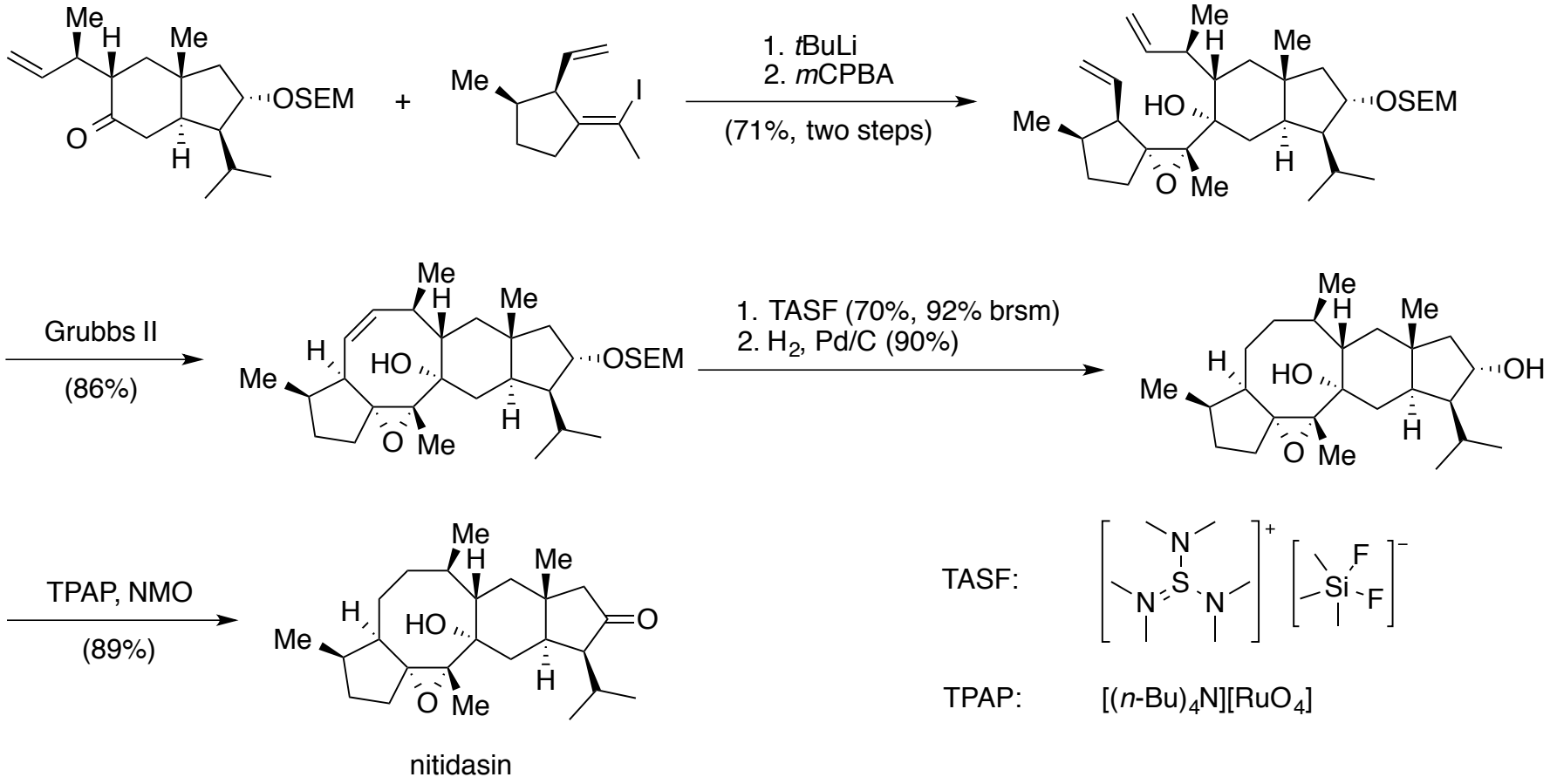
Synthesis V
Model Studies, Addition of Vinyl Lithium to Carbonyl



- Tetrasubstituted alkenyl lithium species are **rarely used** in synthesis
- Addition is **highly stereoselective** with respect to the *trans*-hydrindanone
- RCM before epoxidation resulted in formation of **cyclopentene**
- First epoxidation → virtually **no** epoxidation of terminal double bonds observed, clean, chemo- and stereoselective (even with large excess of reagent)

Synthesis VI

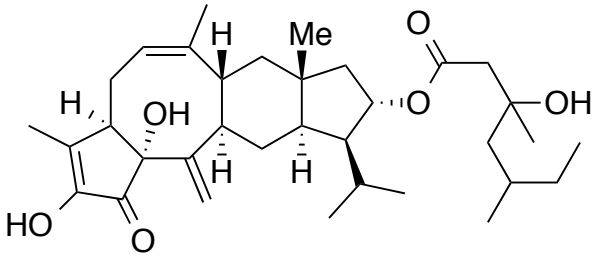
Applying Model Studies, Finishing the Synthesis



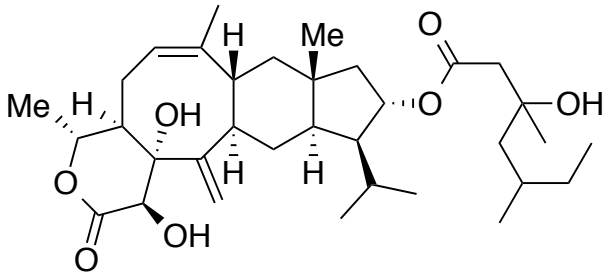
- Hydrogenation after RCM → leading to sensitive substrate
- Carefully prepared acid-free $CDCl_3$ for NMR

Conclusion

- Development of **first total synthesis** of nitdasin in **22 linear steps** (overall yield: 4%)
- Several **high diastereoselective** transformations for **ten** stereogenic centres
  - Addition of complex tetrasubstituted **alkenyl lithium** compound
- Efficient **RCM** to form highly substituted 8-membered ring
  - Benefits from conformational **pre-organisation** of substrate
- Total synthesis of **YW-compounds** (inhibitor of mammalian GPI-anchor biosynthesis) under investigation

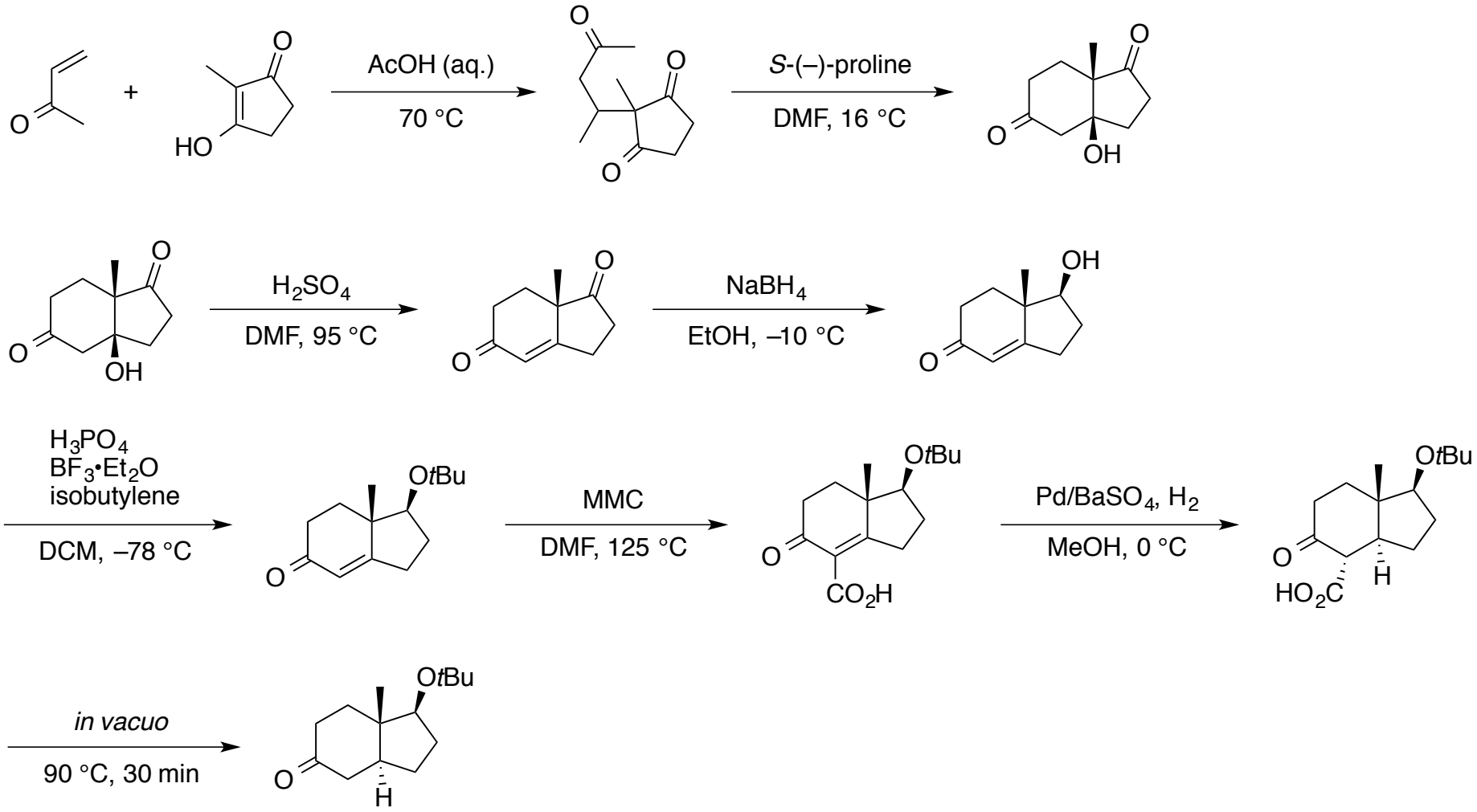


YW-3699



YW-3548

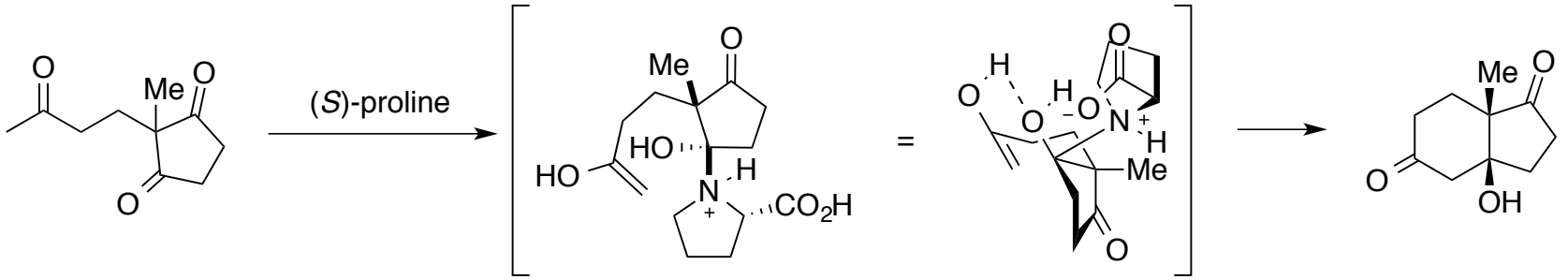
Supplementary Information
Synthesis of Starting Ketone



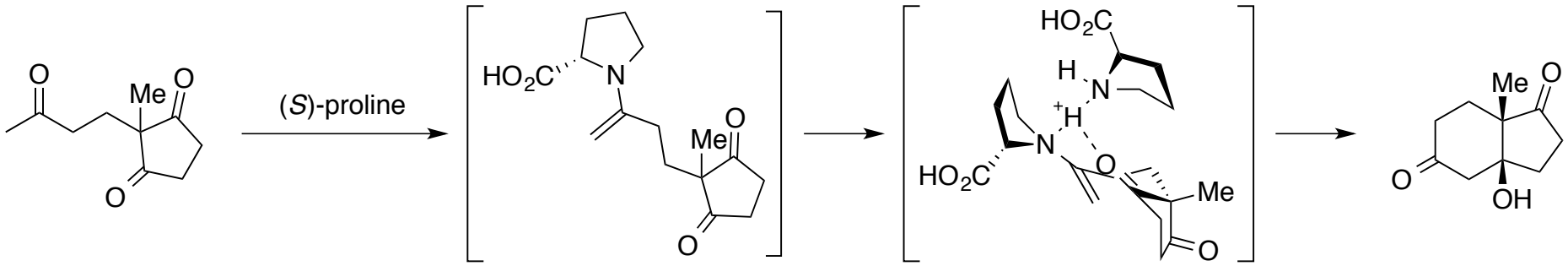
Z. G. Hajos, D. R. Parrish, *Org. Synth.* **1985**, *63*, 26–31
R. A. Micheli *et al.*, *J. Org. Chem.* **1975**, *40*, 675–681

Supplementary Information
(*S*)-Proline Catalysis

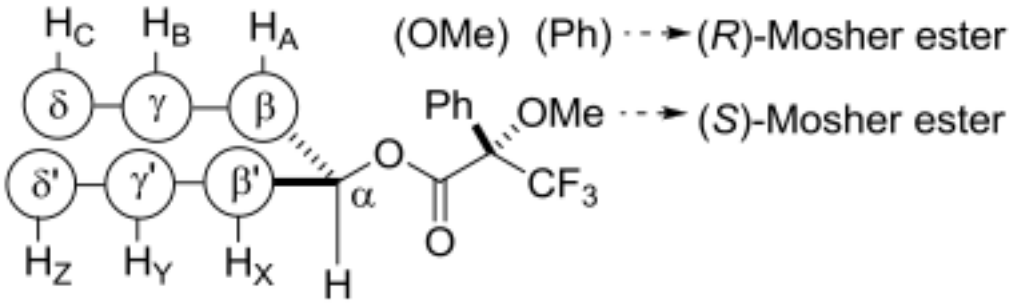
First Mechanistic Proposal



Dual Proline Model



Supplementary Information
Mosher-Ester Analysis

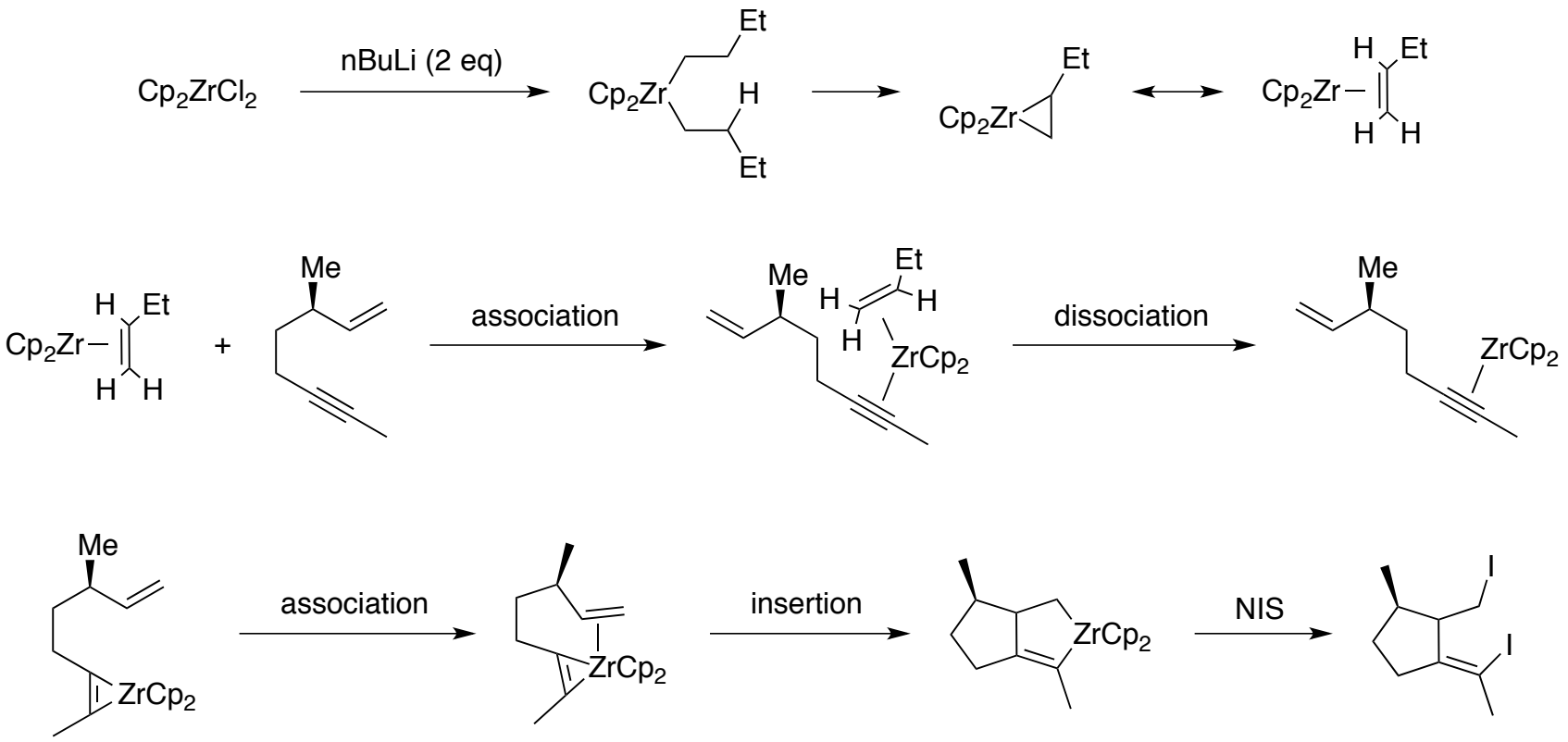


H_A, H_B, H_C: $\delta_S - \delta_R$ = +ve

H_X, H_Y, H_Z: $\delta_S - \delta_R$ = –ve

J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem*. **1969**, *34*, 2543–2549
Ohtani, I.; Kusumi, T.; Ishitsuk, M. O.; Kakisawa, H. *Tetrahedron Lett*. **1989**, *30*, 3147–3150

Supplementary Information
Zirconium Mediated Cyclometalation



G. Angel, Z. Owczarzczyk, E.-I. Negishi, *Tetrahedron Lett*. **1992**, *33*, 1543–1546
A. M. Garcia, J. L. Mascarenas, L. Castedo, A. Mourino, *J. Org. Chem*. **1997**, *62*, 6353–6358