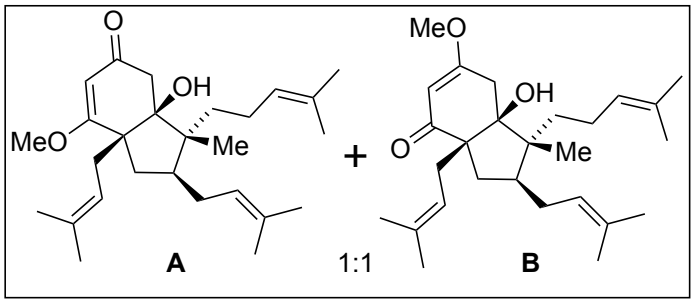
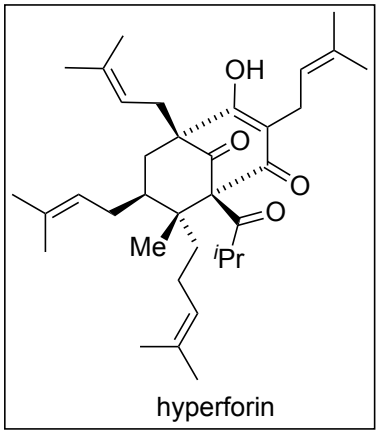
Total Synthesis of Hyperforin

Ting, C. P.; Maimone, T. *J. Am. Chem. Soc.* **2015**, *137*, 10516

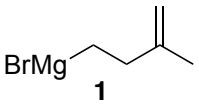
1 – 5



6 – 10



1) **1**, CuBr•DMS, LiCl, TMSCl
2) MeLi•LiI *then* **2**, HMPA *then* TsOH, Δ
3) LDA, prenyl bromide
4) LTMP, **3**
5) $TMSCHN_2$, MeOH, Toluene



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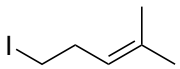

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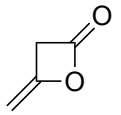

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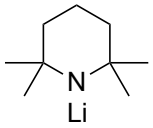


Lithium tetramethyl piperdine (LTMP)

6) $PhI(OAc)_2$, KOH, MeOH
7) LTMP, TsCl
8) LTMP, *i*-PrCOCN,
9) *i*-PrMgBr•LiCl, LDA, Li(2-Th)CuCN, *then* prenyl bromide
10) LiCl, DMSO, Δ

What are the two major types of cuprates?
Gilman - R_2CuLiX or R_2CuMgX
Cyanocuprates - RCu(CN)Li – Less reactive than gilman cuprates
Lipshutz - $R_2Cu(CN)Li_2$ – Higher order cuprates – More reactive – CN acts as dummy ligand

Hint: in step 2 there is also an isomerization

Propose a mechanism for step 4

What is the pK_a of LTMP?
pK_a = 35 for reference LDA is 36

Only one isomer is taken forward. The other can be recycled, how could this be done (2 steps)
NaOH, then $TMSCH_2N_2$ again.

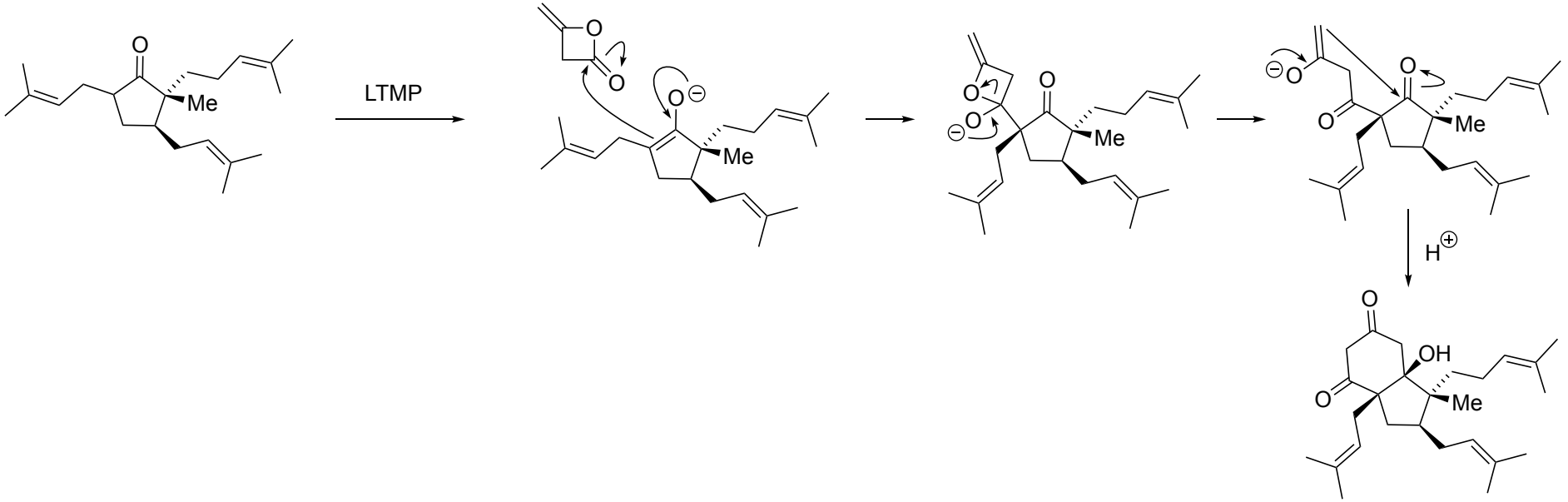
Propose a mechanism for step 6

Hint: Step 7 is a chlorination

Suggest a reason that LDA was added in step 9.
Citation 22 in the main text suggest *i*-PrCl formed as a byproduct which consumes the magnesiate in an E_2 elimination reaction.

LDA is used to suppress this.

Mechanism for step 4:



Mechanism for step 6: