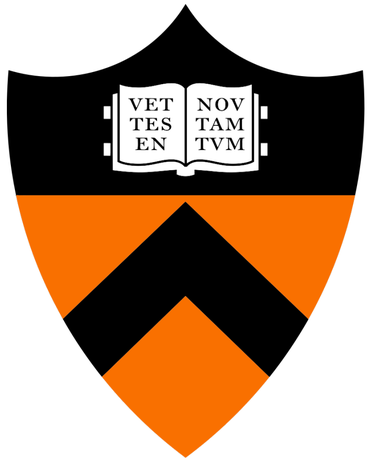
Total Synthesis of Hyperforin: A Quest of Synthetic Efficiency



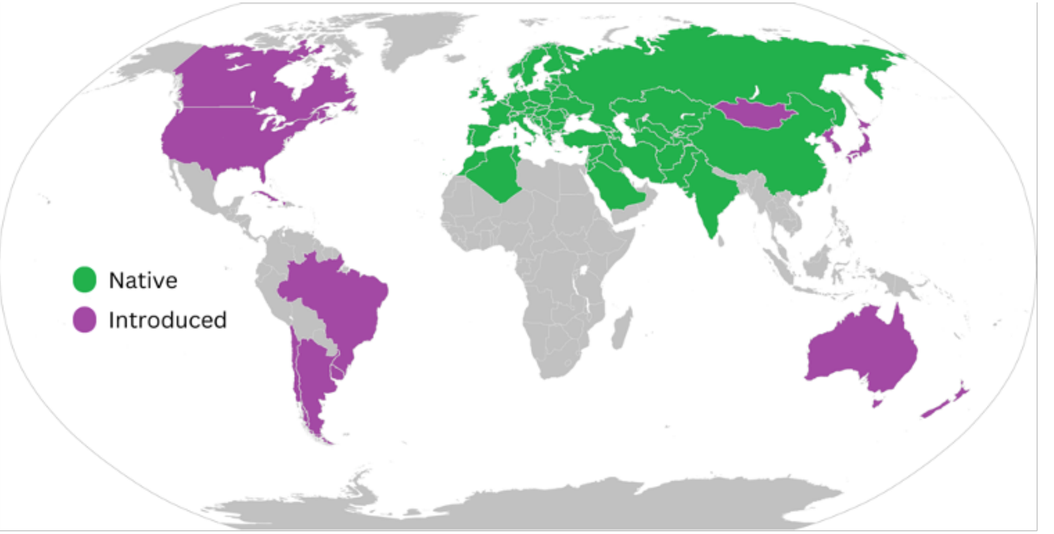
Jiaxin (Jay) Xie

MacMillan Research Group

Oct 24th, 2023

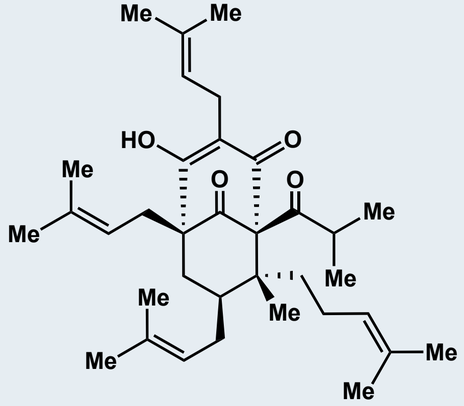
Hyperforin

Hypericum perforatum
(St. John's wort)



Bystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett.* **1975**, *16*, 2791.

Hyperforin



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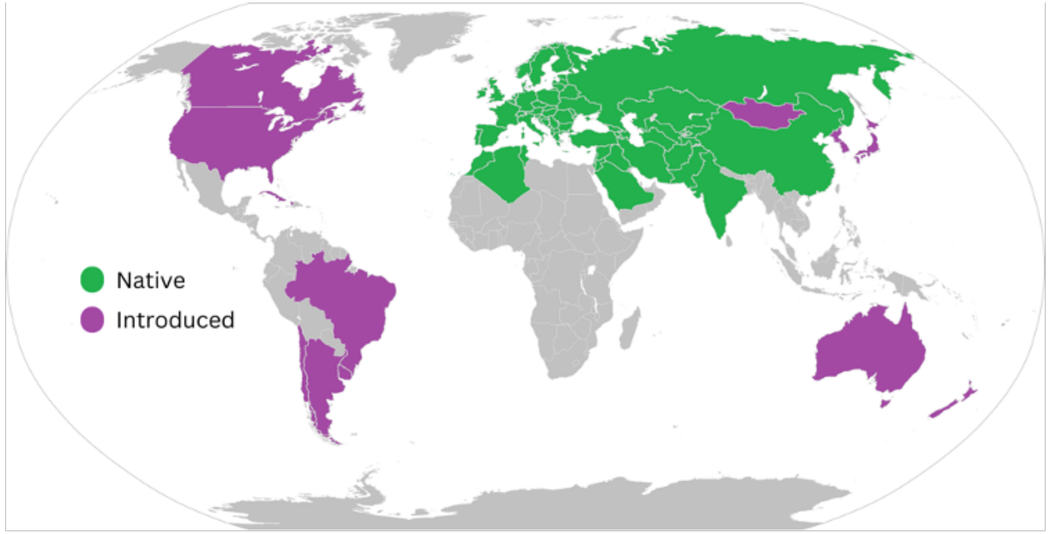

- Isolated from *Hypericum perforatum* in 1971

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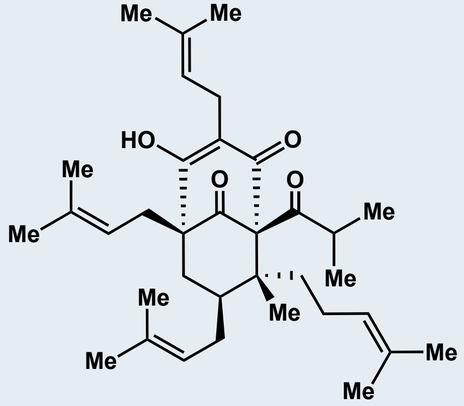

Hyperforin

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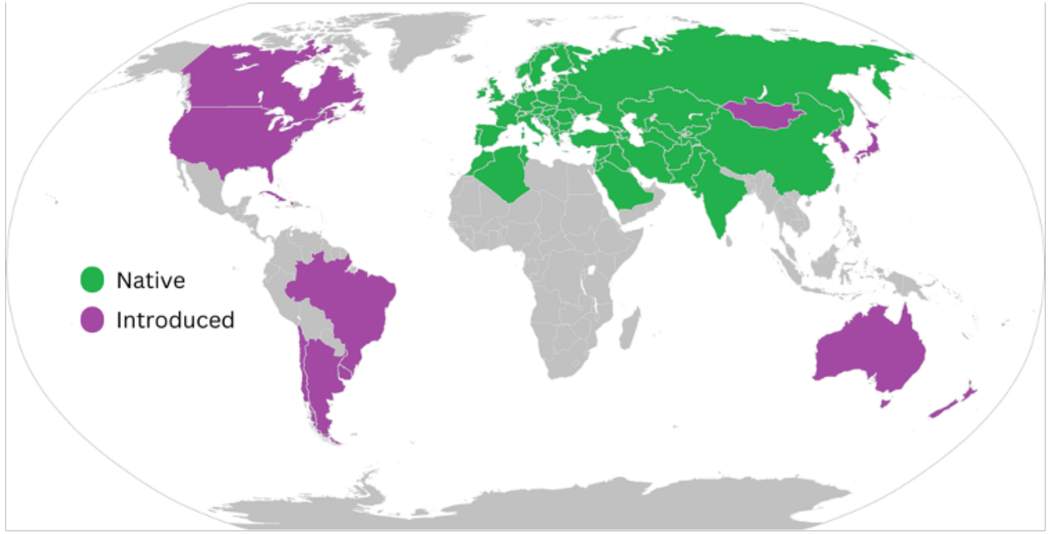

- Isolated from *Hypericum perforatum* in 1971
- Responsible for the **anti-depressant** activity of the herb
- Selectively activate TRPC6 (classical transient receptor potential protein)

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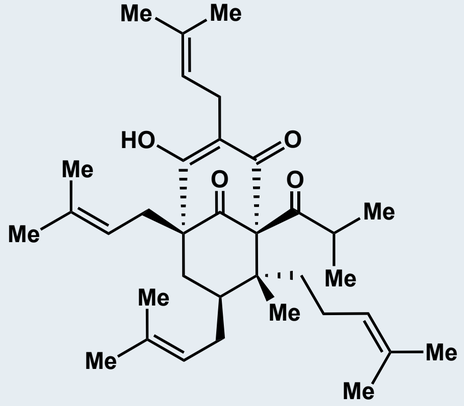

Hyperforin

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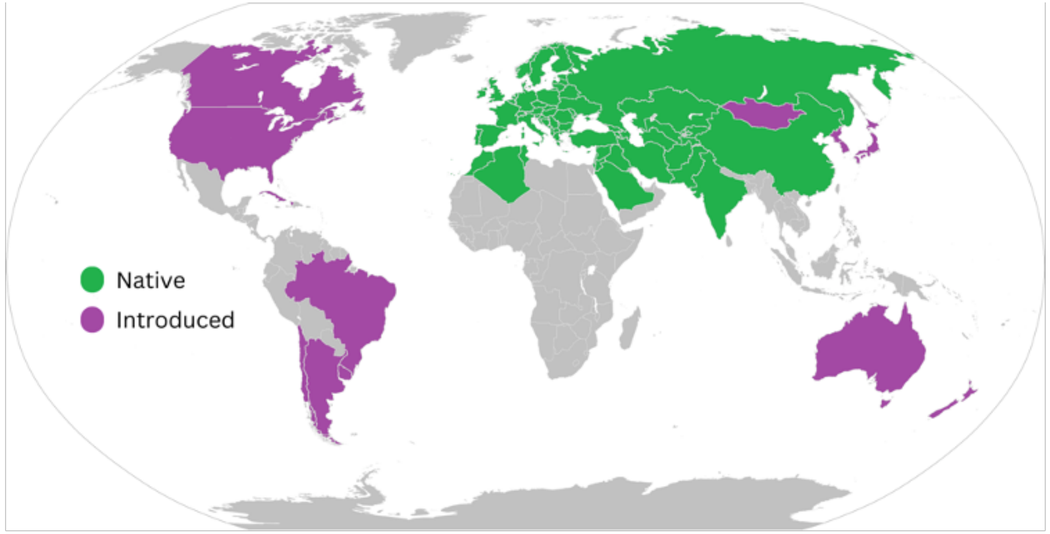
(St. John's wort)



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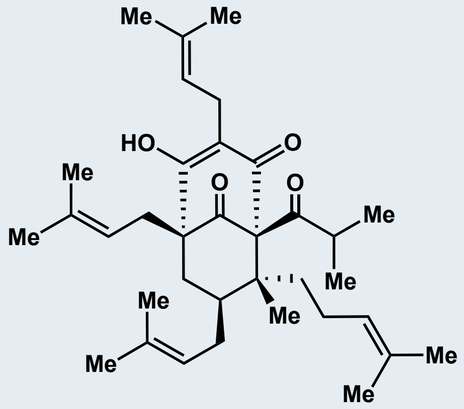
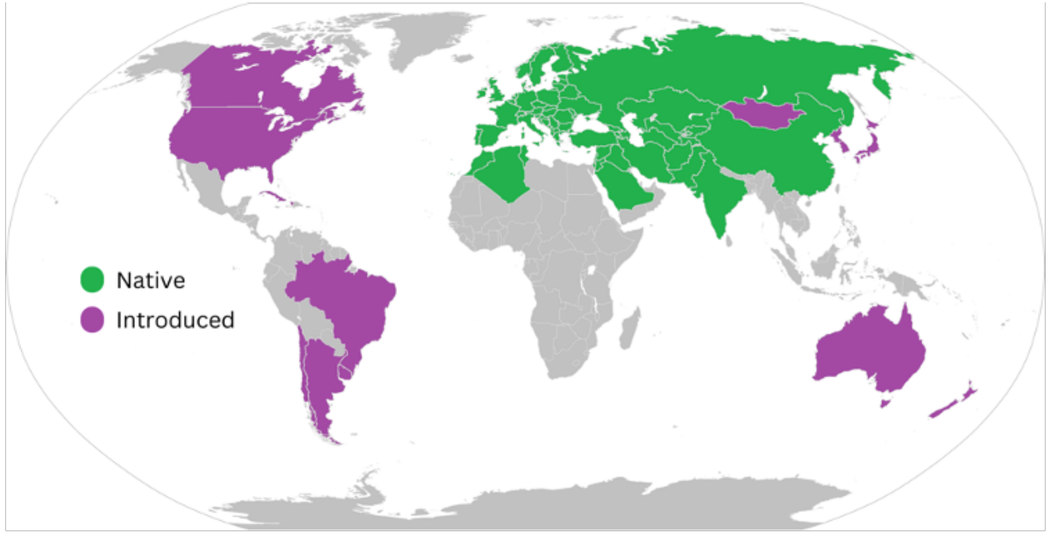
Hyperforin



Hyperforin

Hypericum perforatum
(St. John's wort)



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- Highly oxidized **bicyclo[3.3.1]nonane** core
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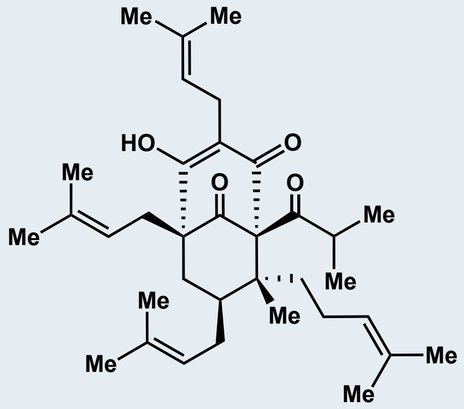
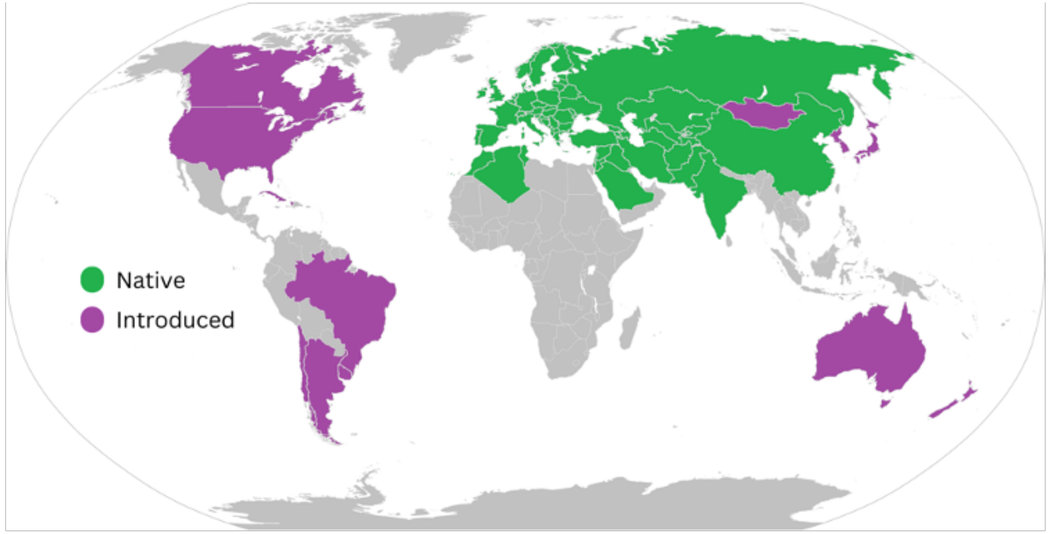
Hyperforin



Hyperforin

Hypericum perforatum
(St. John's wort)



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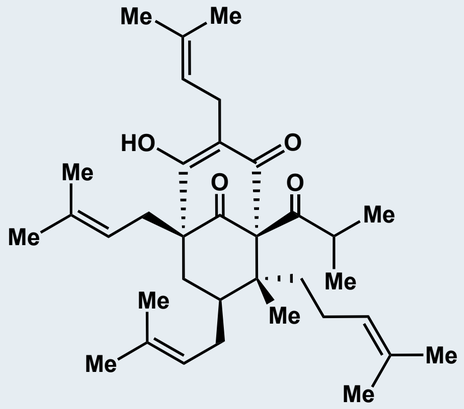
- **P**olycyclic **P**olyprenylated **A**cyl**p**hloroglucinols (**PPAP**s)

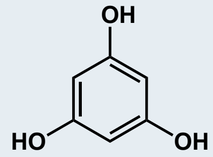
Bystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett.* **1975**, *16*, 2791.

Polycyclic Polyprenylated Acylphloroglucinols (PPAPs)



Hyperforin

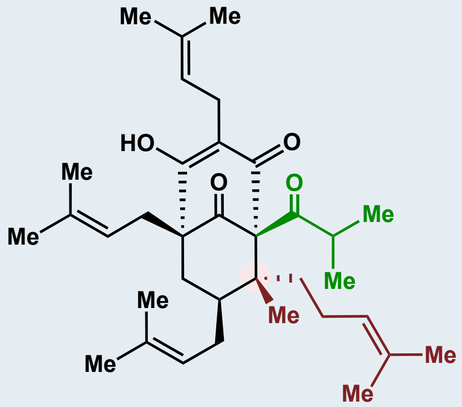
Hypericum perforatum
(St. John's wort)



Phloroglucinol

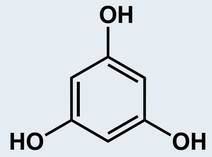
Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.

Polycyclic Polyprenylated Acylphloroglucinols (PPAPs)

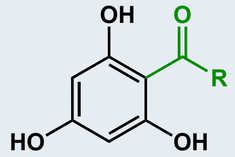


Hyperforin

Hypericum perforatum
(St. John's wort)



Phloroglucinol



Acylphloroglucinol

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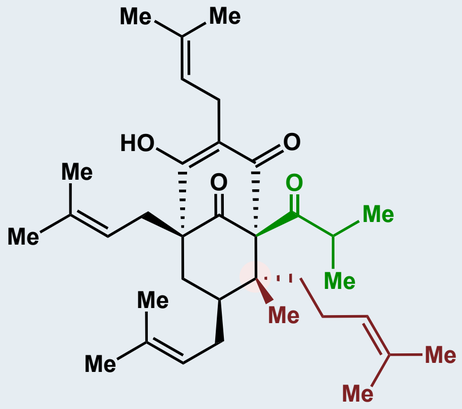
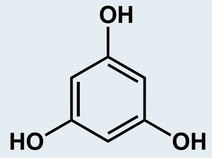
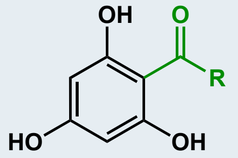


Hyperforin

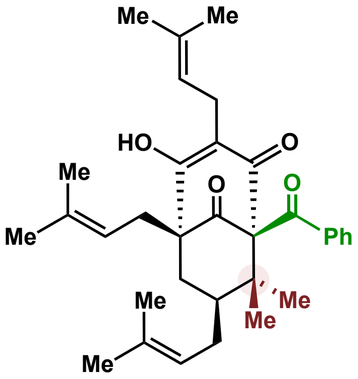
Hypericum perforatum
(St. John's wort)



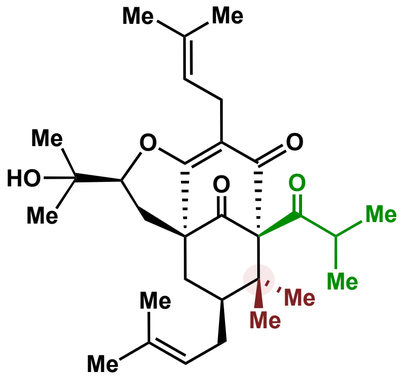
Phloroglucinol



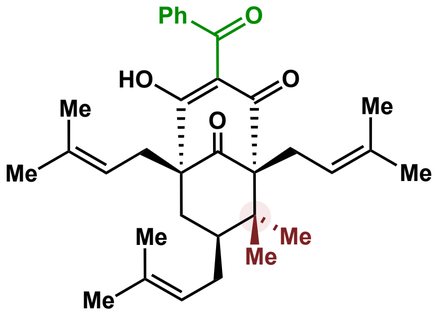
Acylphloroglucinol



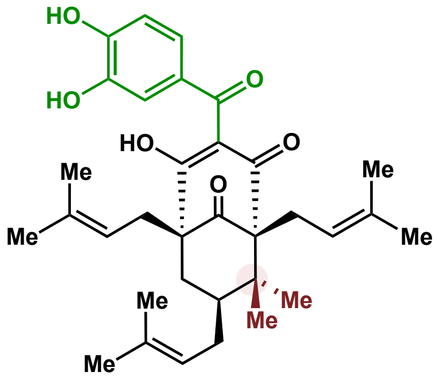
Nemorosone



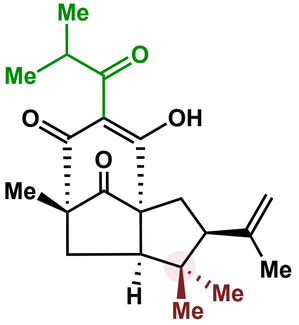
Garsubellin A



Clusianone



Aristophenone A



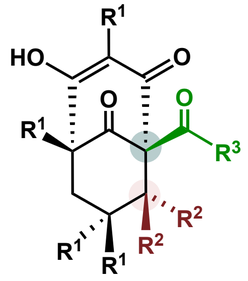
Lalibinone D

- Isolated mainly from *Hypericum perforatum* and other plants from the *Guttiferae* family
- Over 150 natural products discovered by 2006

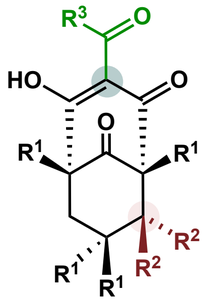
Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.

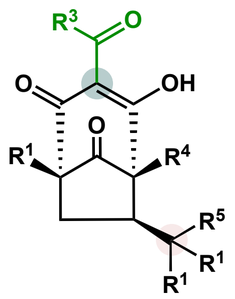
Biosynthesis of PPAPs

Type A

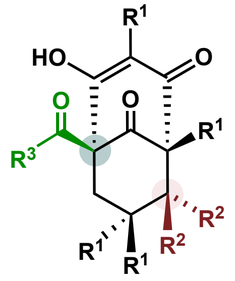


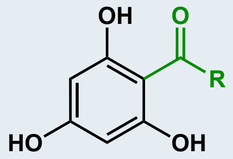
Type B





Type C





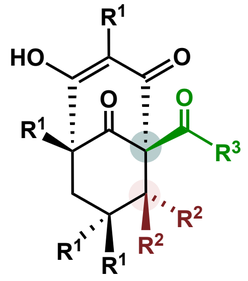
Acylphloroglucinol

(R = *i*-Pr, Ph)

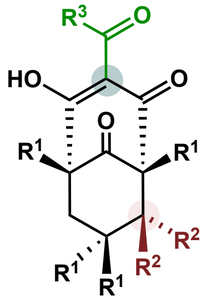
Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.

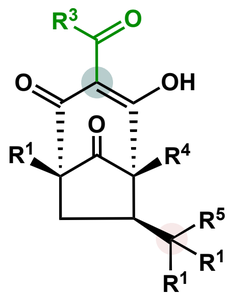
Biosynthesis of PPAPs

Type A



Type B





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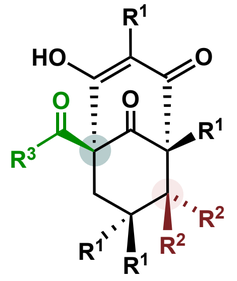
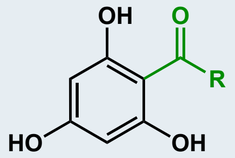
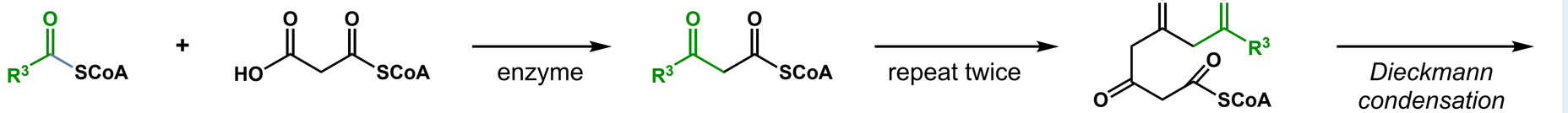




Acylphloroglucinol
(R = *i*-Pr, Ph)

Synthesis of Acylphloroglucinols



Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.

Biosynthesis of PPAPs

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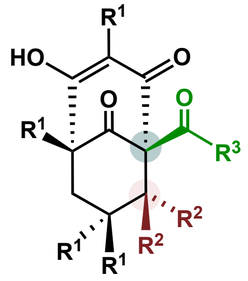
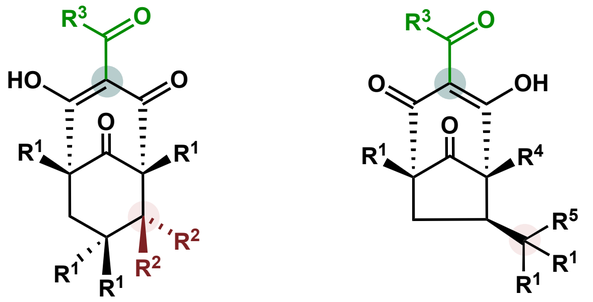


Type B



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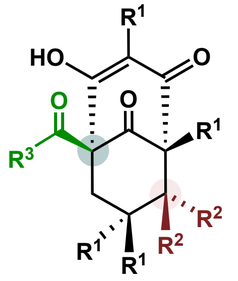
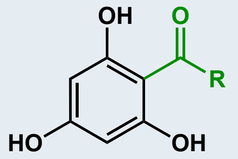
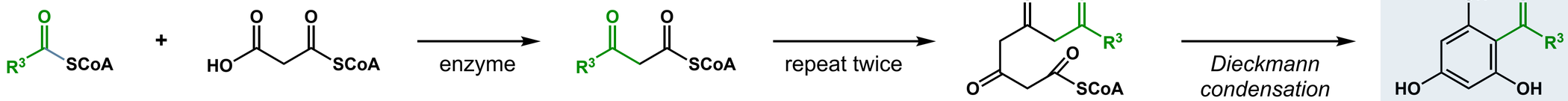




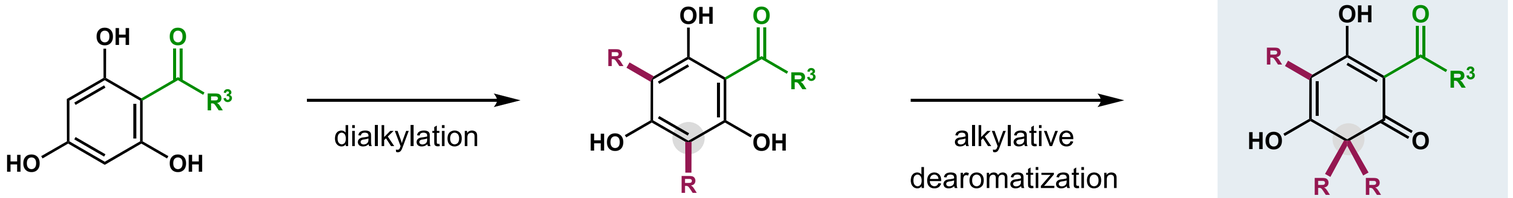
Acylphloroglucinol

(R = *i*-Pr, Ph)

Synthesis of Acylphloroglucinols



Synthesis of Monocyclic Polyprenylated Acylphloroglucinols (MPAPs)



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Biosynthesis of PPAPs

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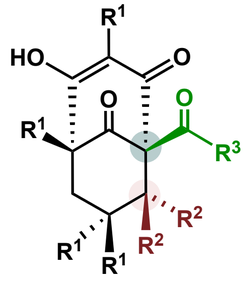
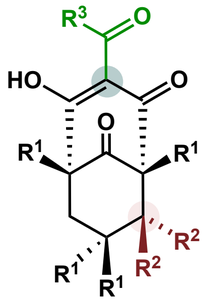
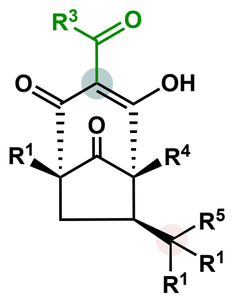
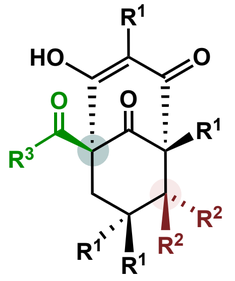


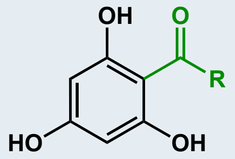
Type B





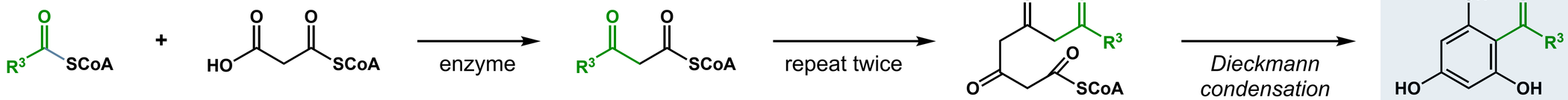
Type C



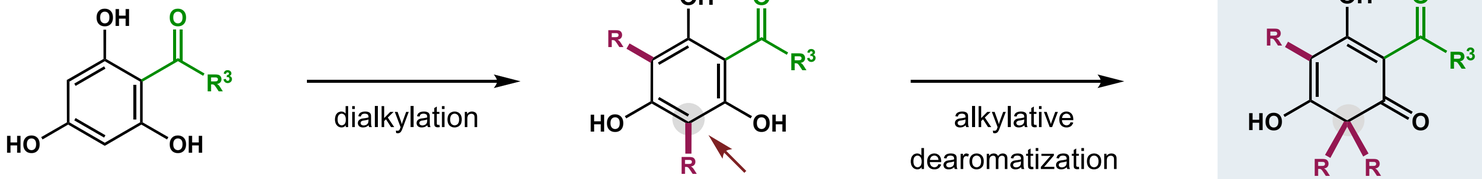


Acylphloroglucinol
(R = *i*-Pr, Ph)

Synthesis of Acylphloroglucinols



Synthesis of Monocyclic Polyprenylated Acylphloroglucinols (MPAPs)



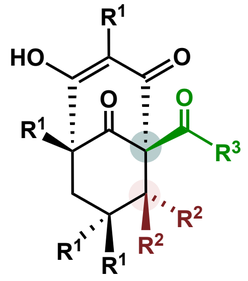
(R = prenyl, geranyl)

Type A/B MPAPs

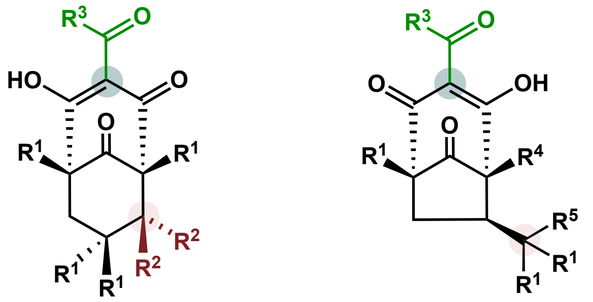
Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.

Biosynthesis of PPAPs

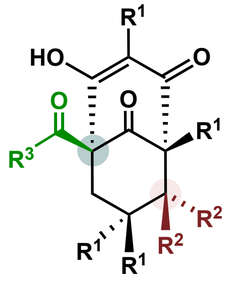
Type A

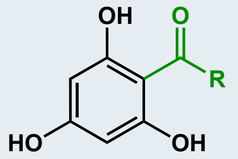


Type B



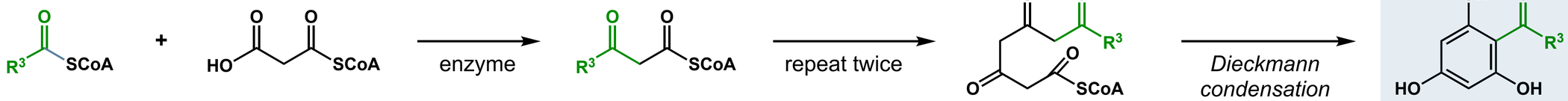
Type C



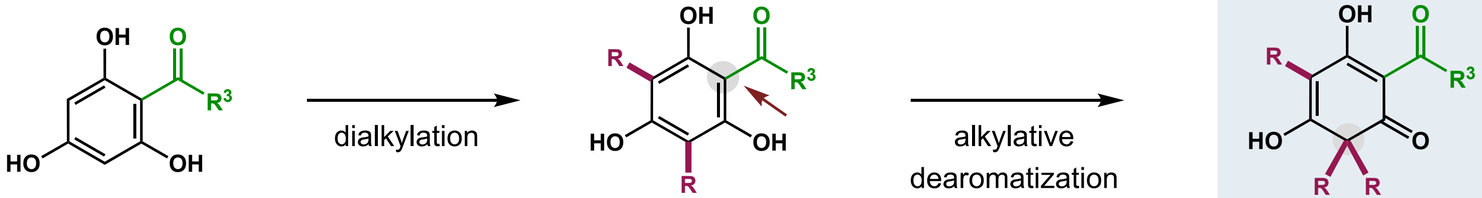


Acylphloroglucinol
(R = *i*-Pr, Ph)

Synthesis of Acylphloroglucinols



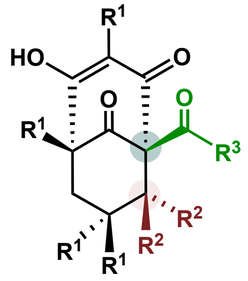
Synthesis of Monocyclic Polyprenylated Acylphloroglucinols (MPAPs)



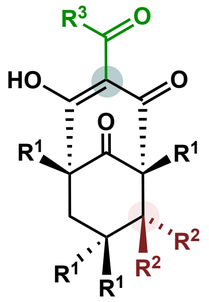
Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.

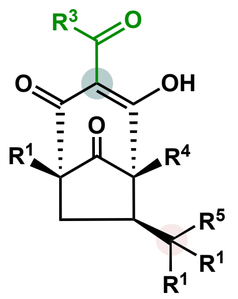
Biosynthesis of PPAPs

Type A

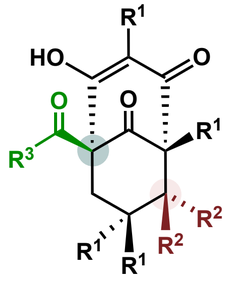


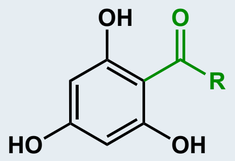
Type B





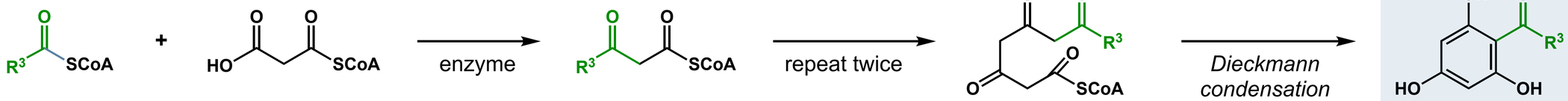
Type C



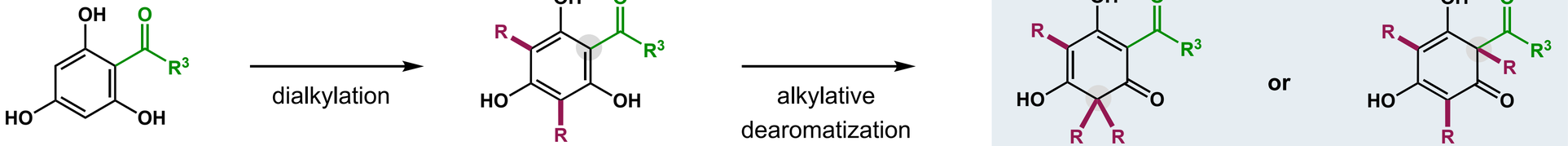


Acylphloroglucinol
(R = *i*-Pr, Ph)

Synthesis of Acylphloroglucinols



Synthesis of Monocyclic Polyprenylated Acylphloroglucinols (MPAPs)



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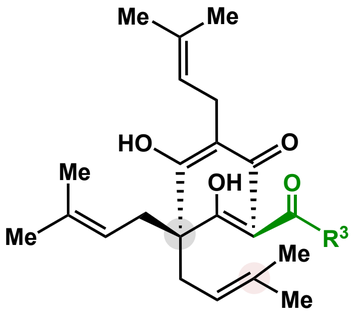
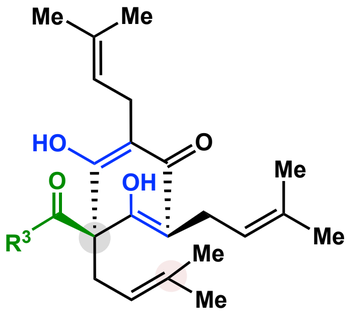
Biosynthesis of PPAPs

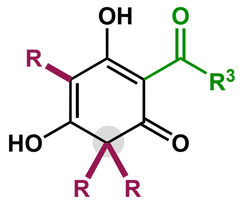
Synthesis of PPAPs from MPAPs



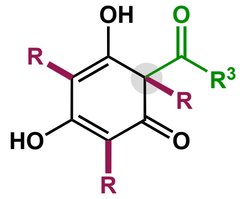
Type A/B MPAPs



Type C MPAPs



Type A/B MPAPs



Type C MPAPs

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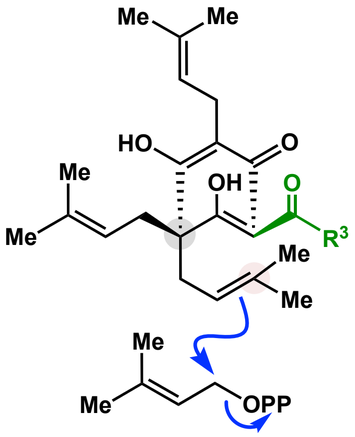
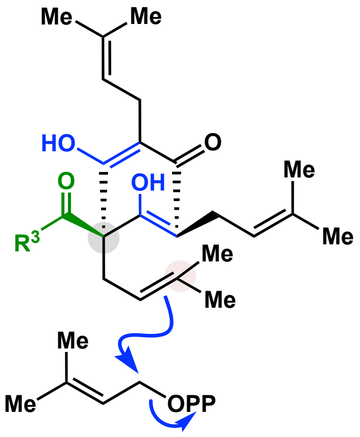
Biosynthesis of PPAPs

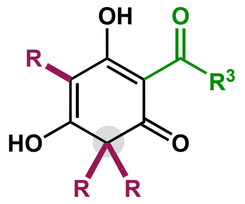
Synthesis of PPAPs from MPAPs



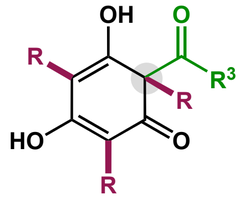
Type A/B MPAPs



Type C MPAPs



Type A/B MPAPs



Type C MPAPs

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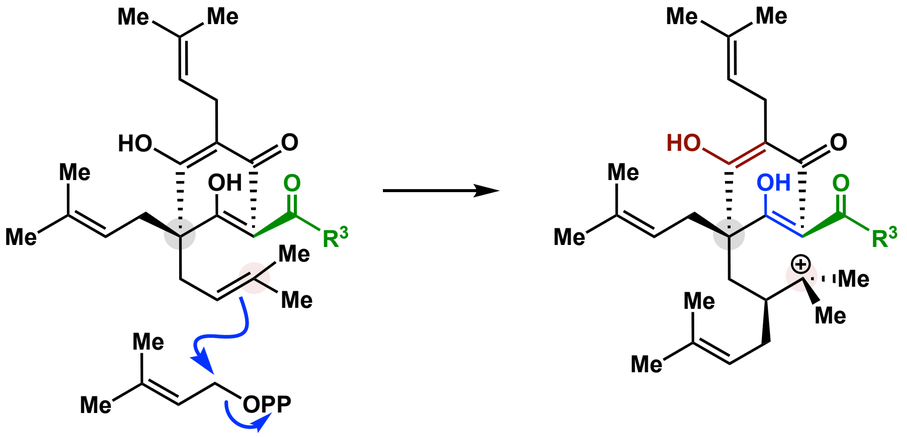
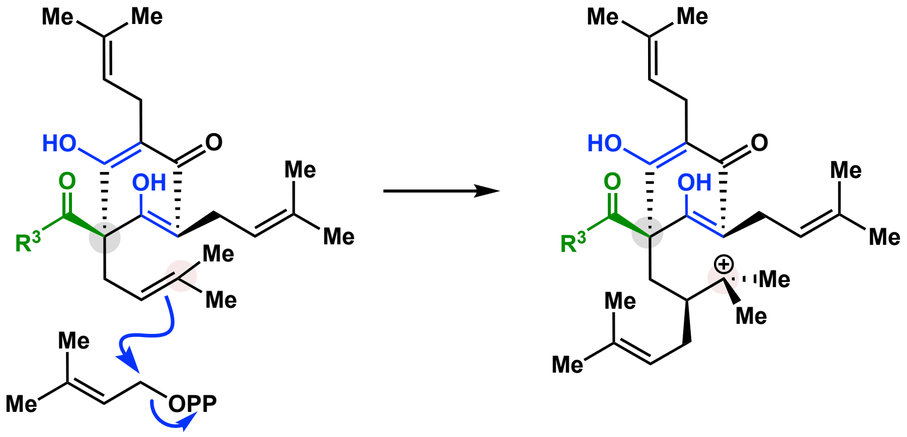
Biosynthesis of PPAPs

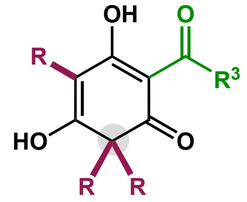
Synthesis of PPAPs from MPAPs



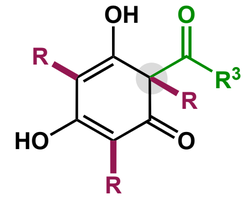
Type A/B MPAPs



Type C MPAPs



Type A/B MPAPs

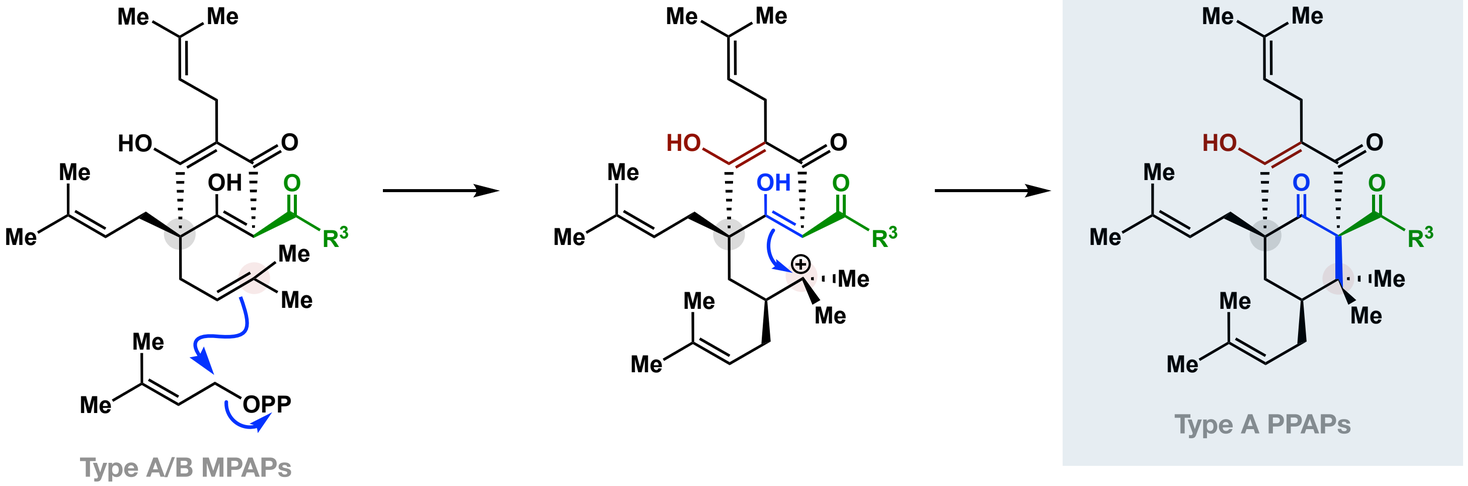


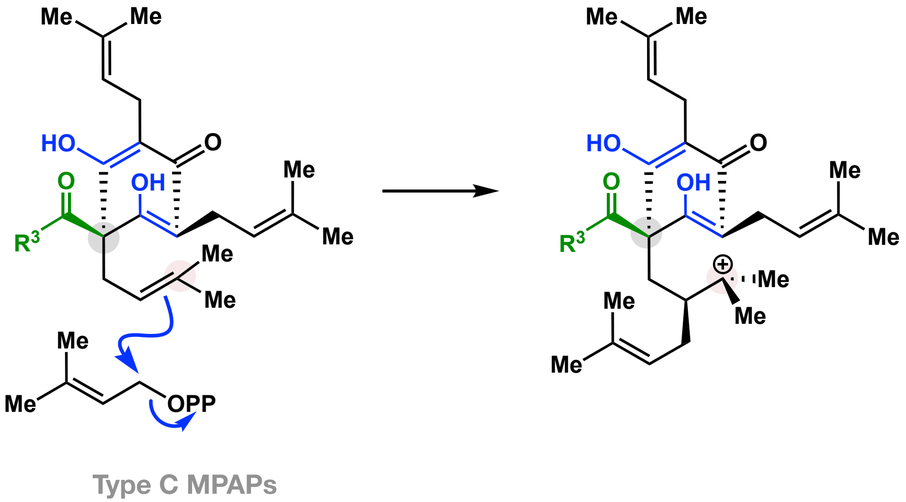
Type C MPAPs

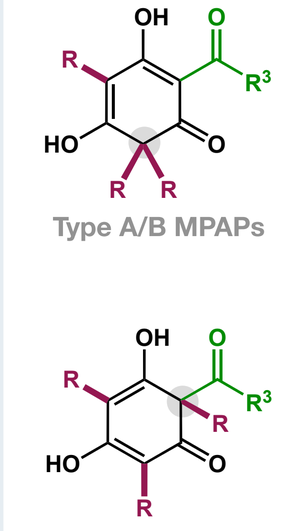
Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.

Biosynthesis of PPAPs

Synthesis of PPAPs from MPAPs







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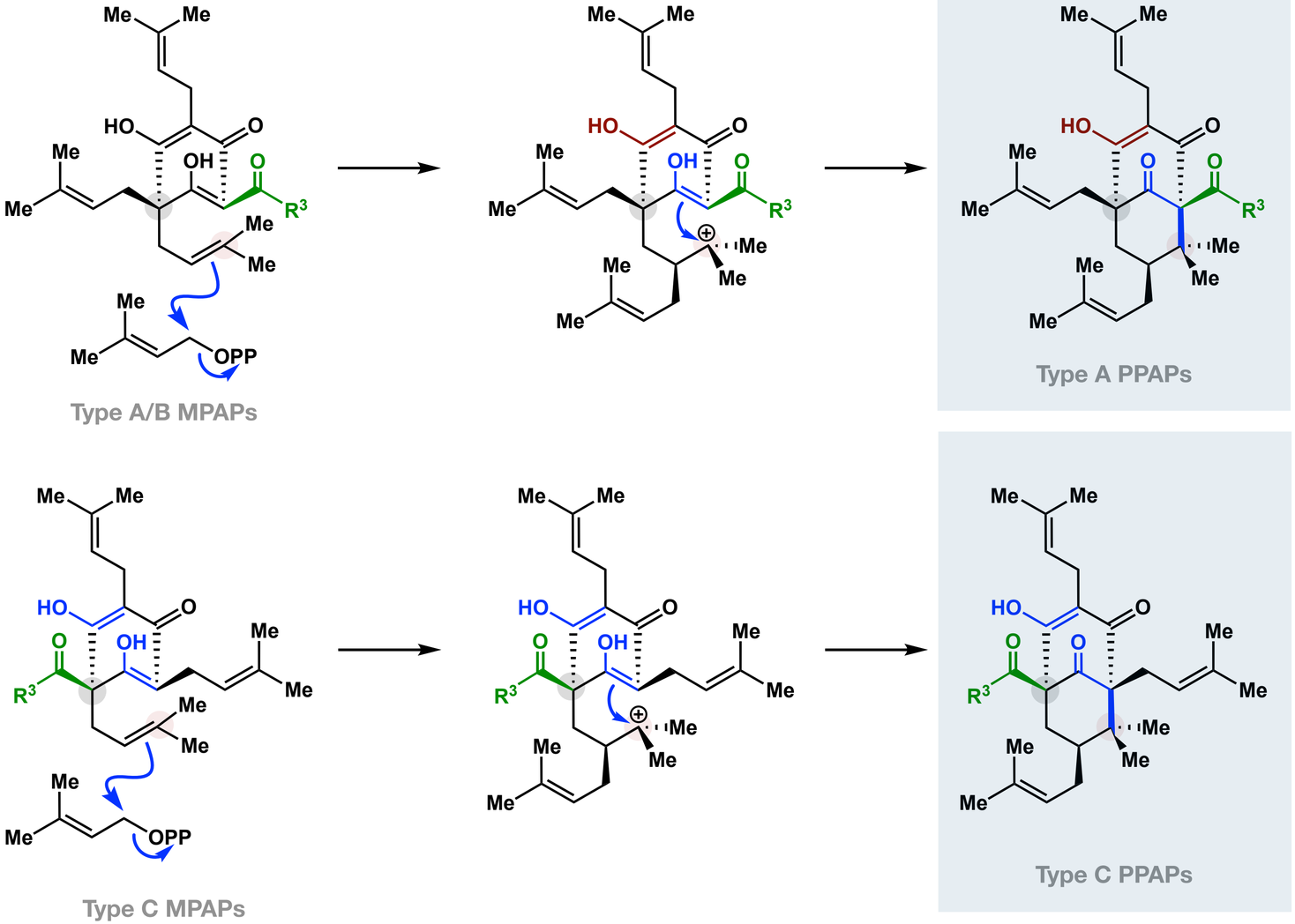
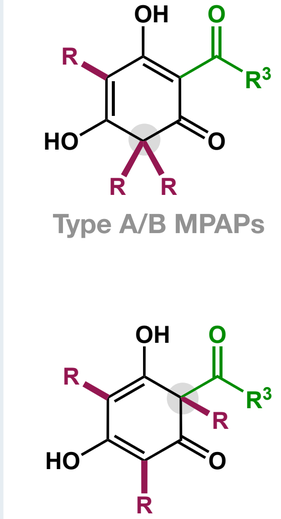
Biosynthesis of PPAPs

Synthesis of PPAPs from MPAPs





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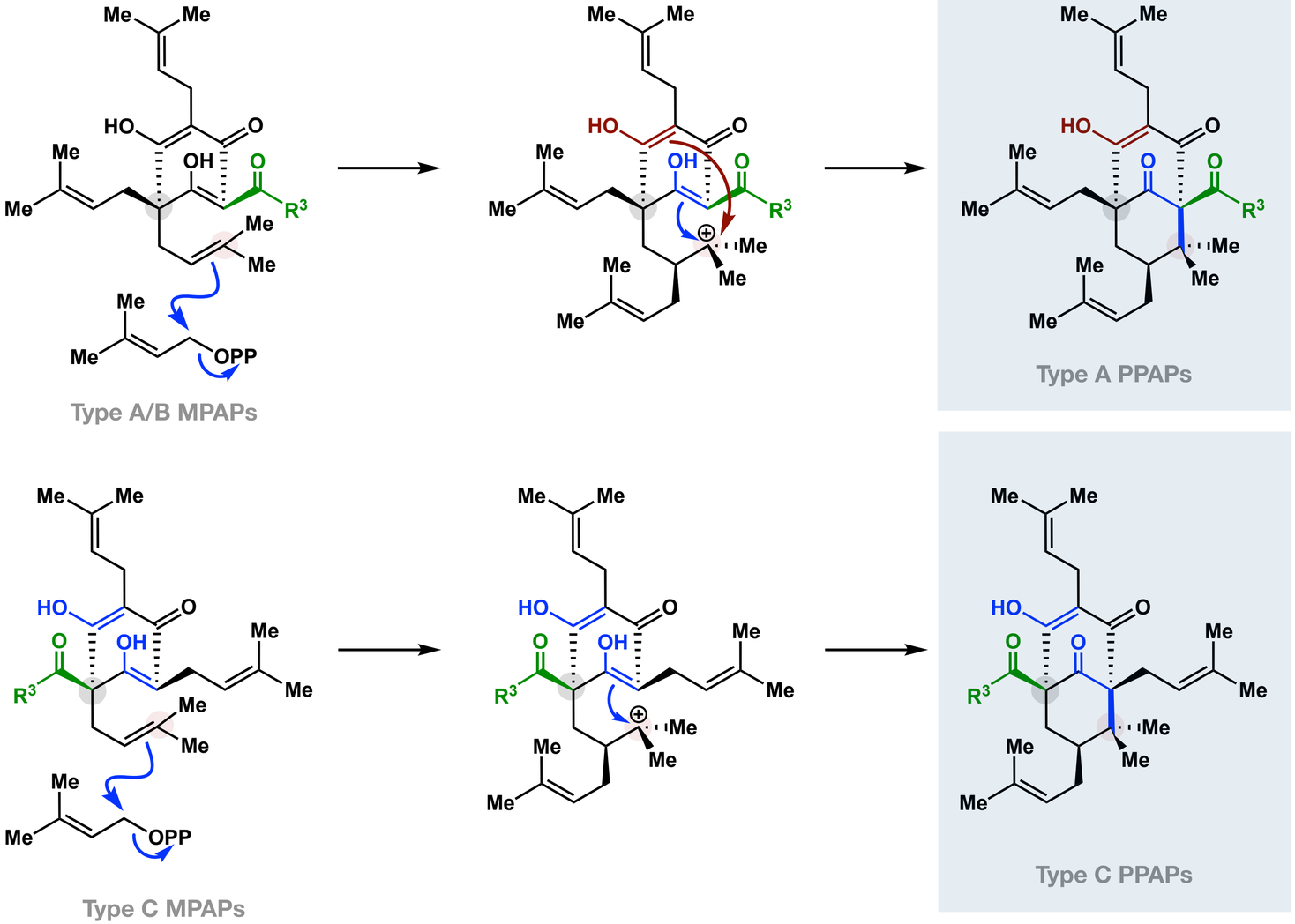
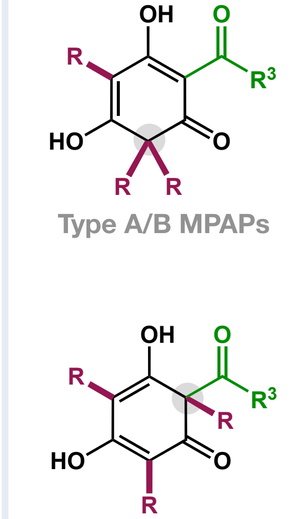
Biosynthesis of PPAPs

Synthesis of PPAPs from MPAPs





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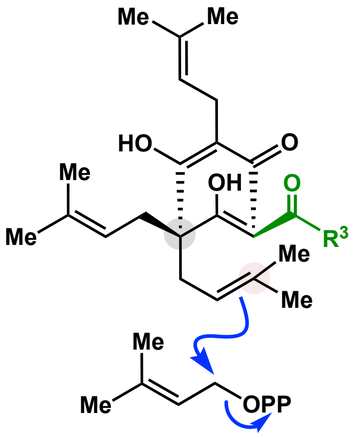
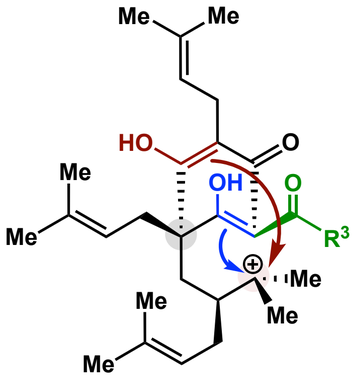
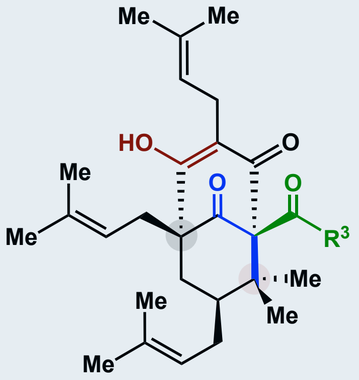
Biosynthesis of PPAPs

Synthesis of PPAPs from MPAPs

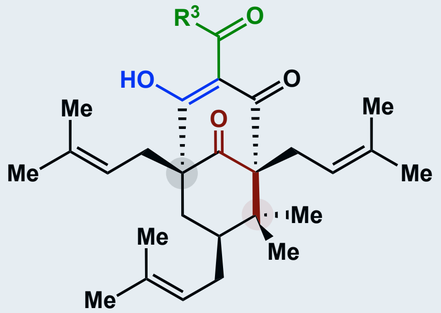


Type A/B MPAPs

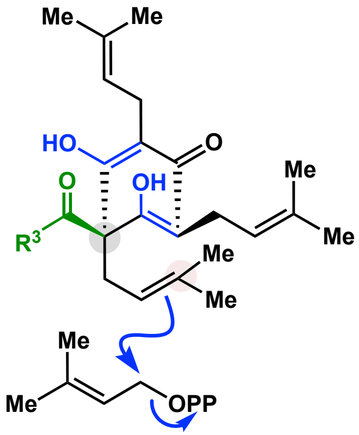




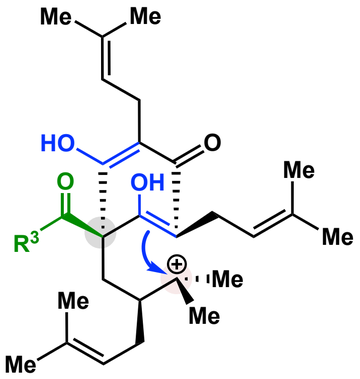
Type A PPAPs

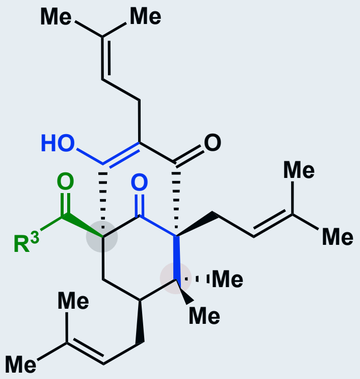


Type B PPAPs

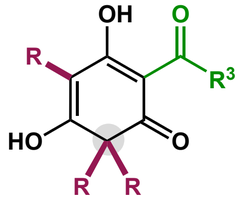


Type C MPAPs

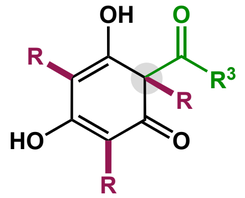




Type C PPAPs



Type A/B MPAPs



Type C MPAPs

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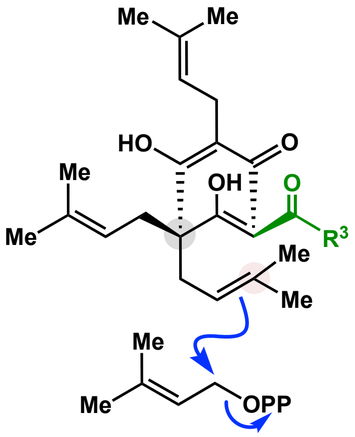
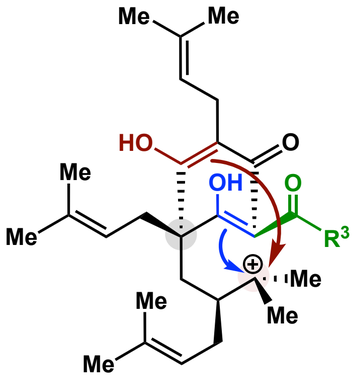
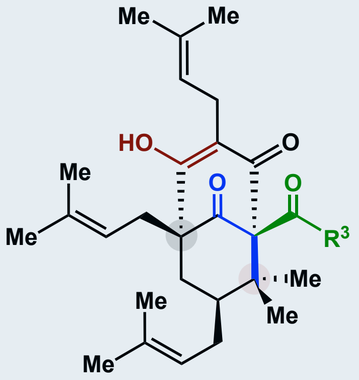
Biosynthesis of PPAPs

Synthesis of PPAPs from MPAPs

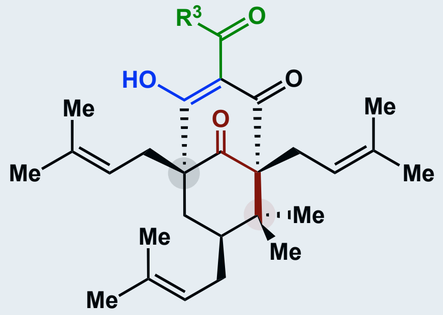


Type A/B MPAPs

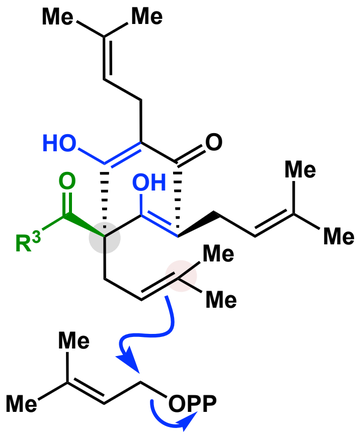




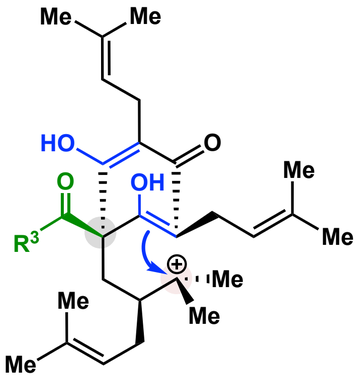
Type A PPAPs

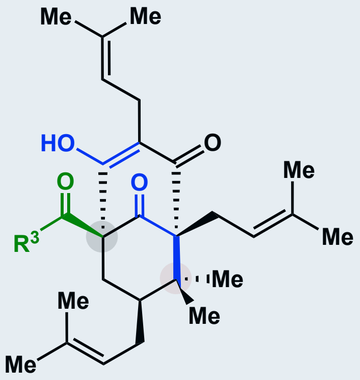


Type B PPAPs

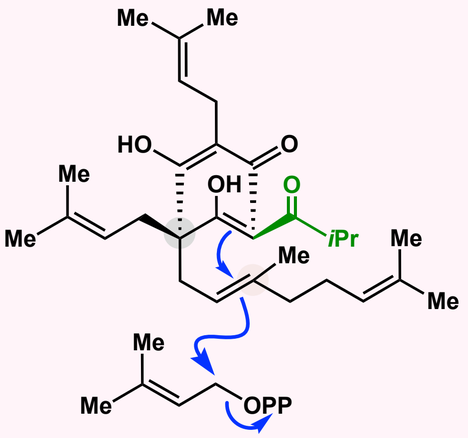


Type C MPAPs

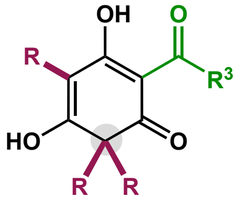




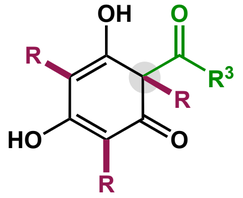
Type C PPAPs



Hyperforin Biosynthesis (Type A)



Type A/B MPAPs



Type C MPAPs

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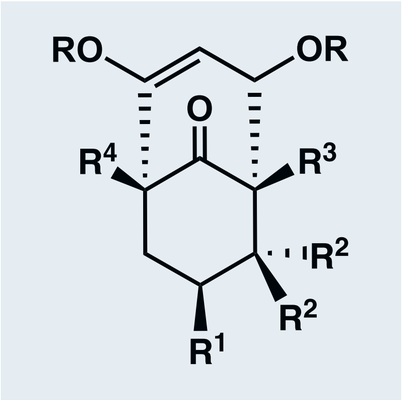
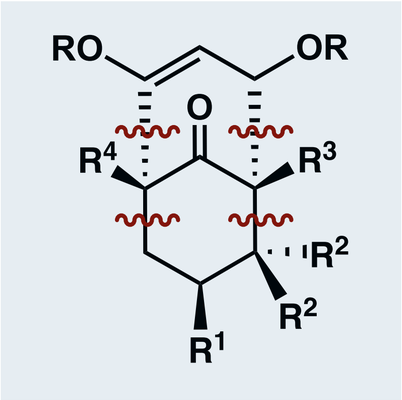
Synthetic Strategies towards Bicyclo[3.3.1]nonane



Richard, J.-A.; Pouwer, R. H.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.* **2012**, *51*, 4536.

Synthetic Strategies towards Bicyclo[3.3.1]nonane



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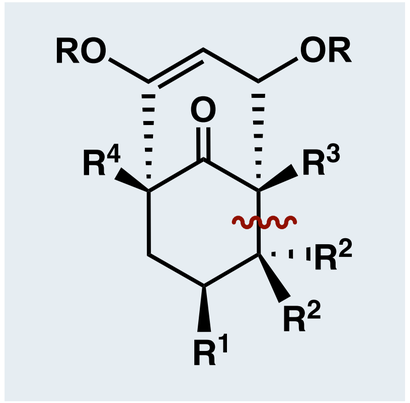
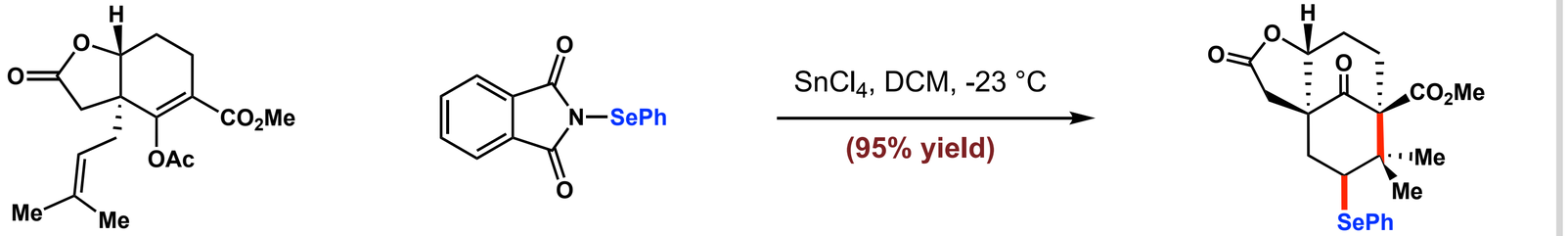
Synthetic Strategies towards Bicyclo[3.3.1]nonane

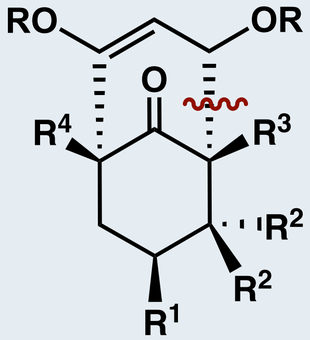


Nicolaou (1999): Selenium-mediated Cyclization

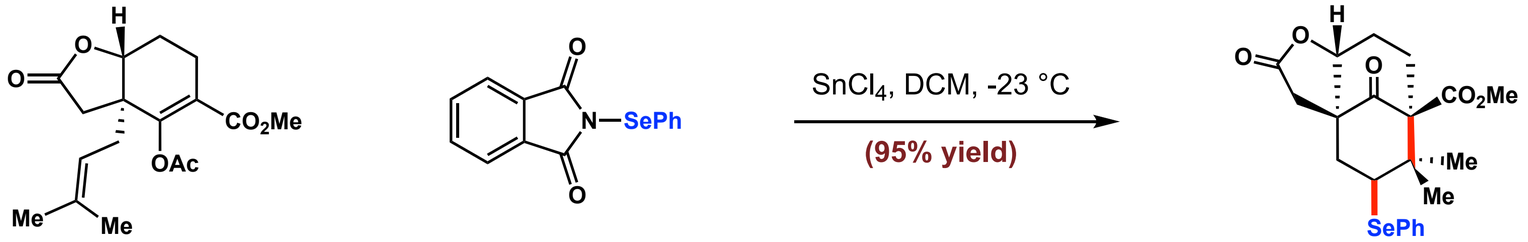


Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724.

Synthetic Strategies towards Bicyclo[3.3.1]nonane

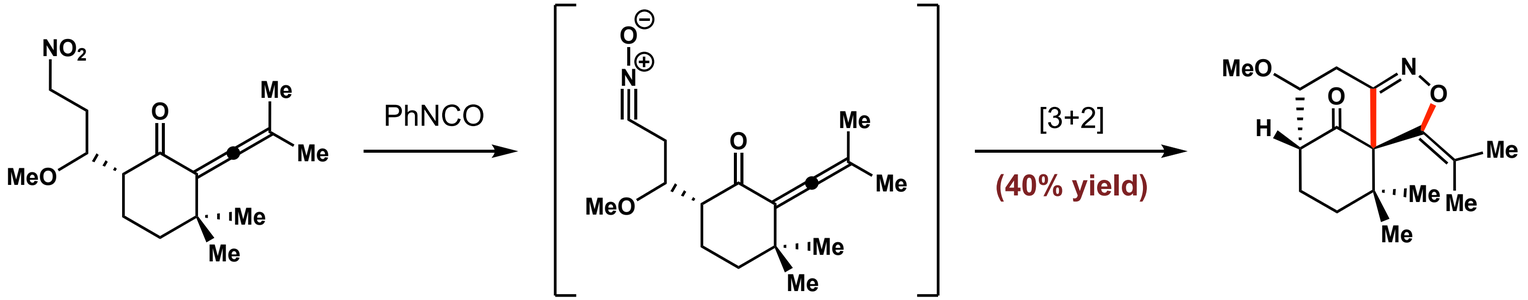


Nicolaou (1999): Selenium-mediated Cyclization



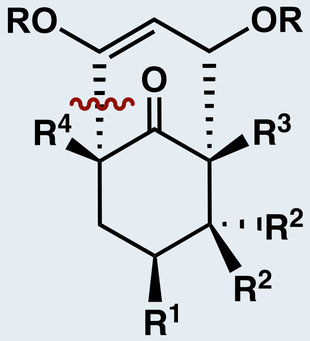
Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724.

Young (2002): Intramolecular [3+2] Cycloaddition

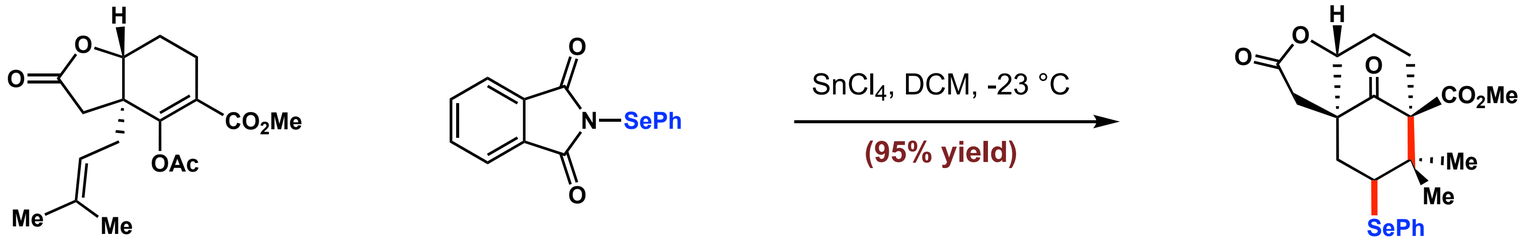


Young, D. G. J.; Zeng, D. *J. Org. Chem.* **2002**, *67*, 3134.

Synthetic Strategies towards Bicyclo[3.3.1]nonane

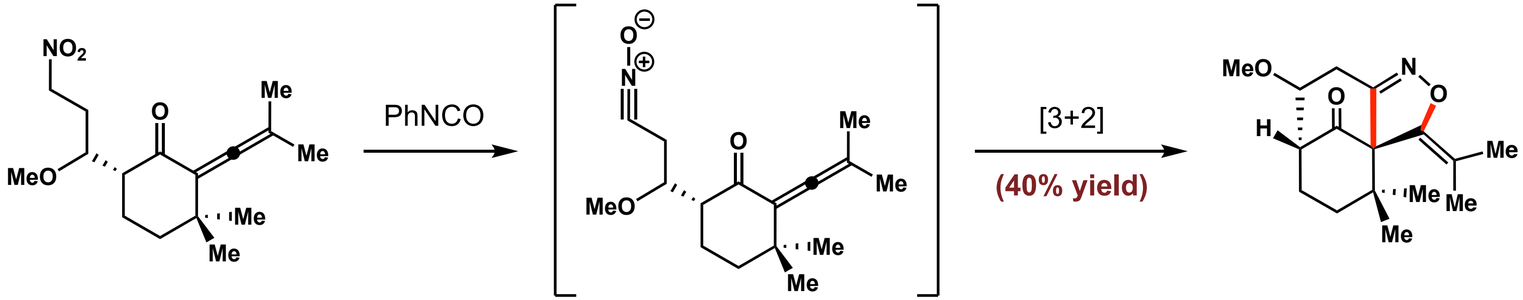


Nicolaou (1999): Selenium-mediated Cyclization



Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724.

Young (2002): Intramolecular [3+2] Cycloaddition



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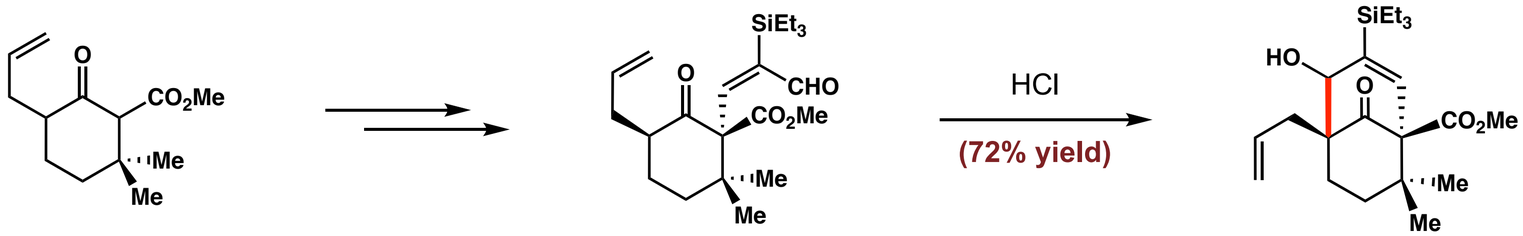
Grossman (2003): Intramolecular Aldol Reaction



Ciochina, R.; Grossman, R. B. *Org. Lett.* **2003**, *5*, 4619.

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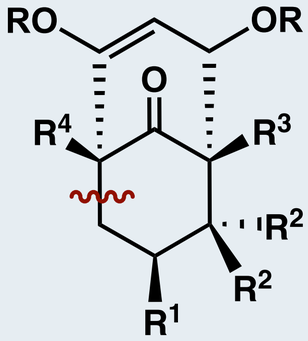
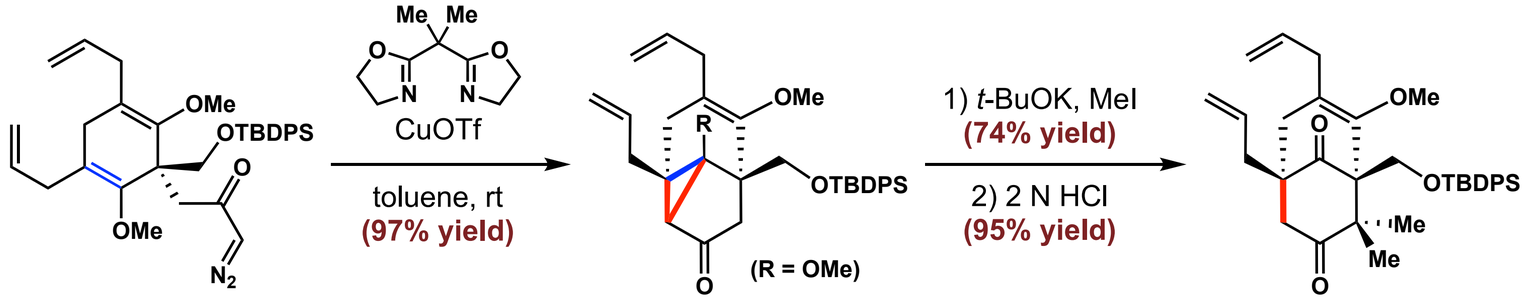


Nakada (2010): Intramolecular Cyclopropanation/Fragmentation



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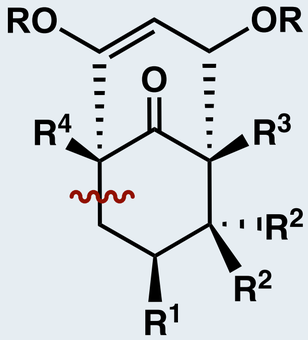

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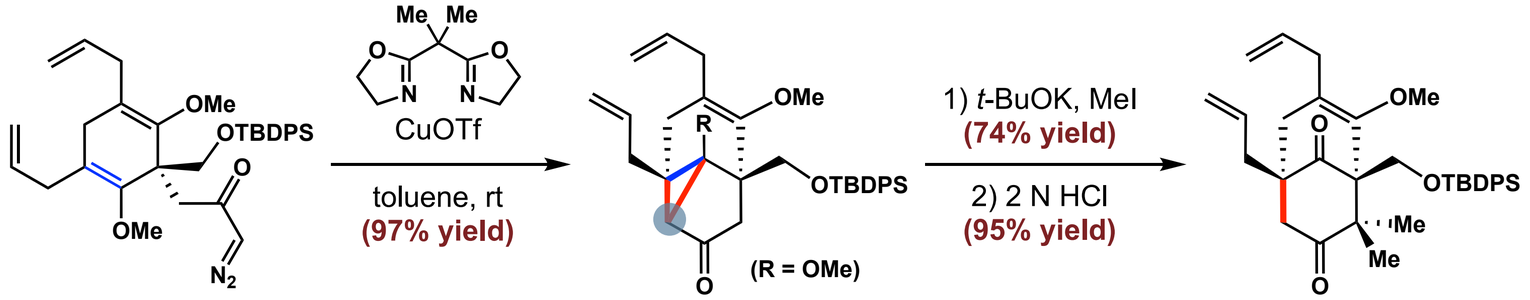

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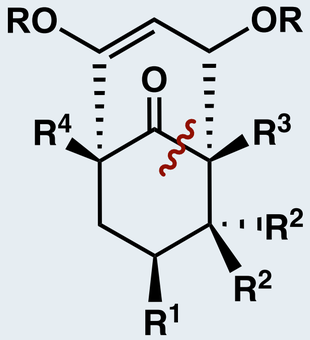

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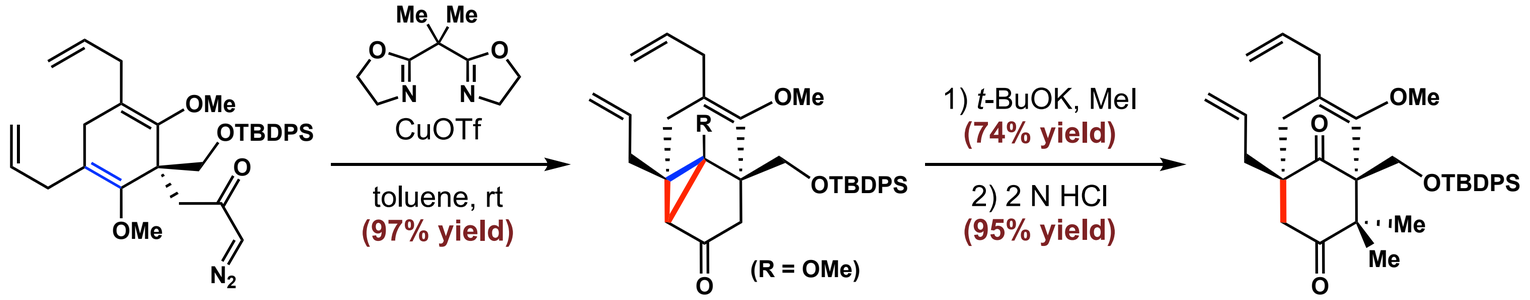

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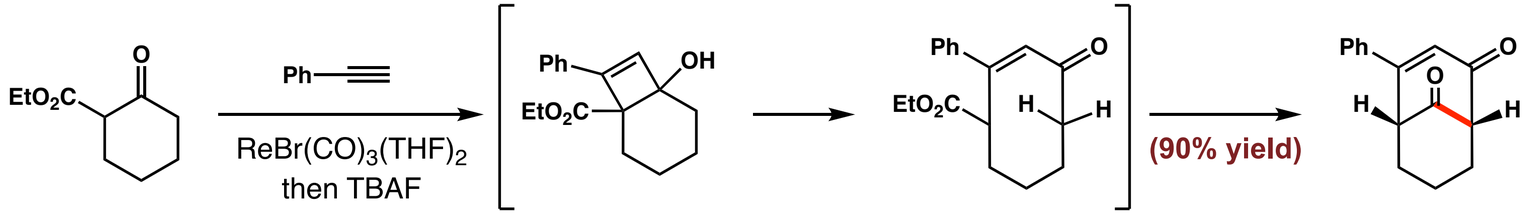

Kuninobu, Y.; Morita, J.; Nishi, M.; Kawata, A.; Takai, K. *Org. Lett.* **2009**, *11*, 2535.

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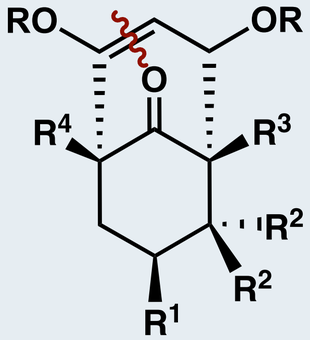

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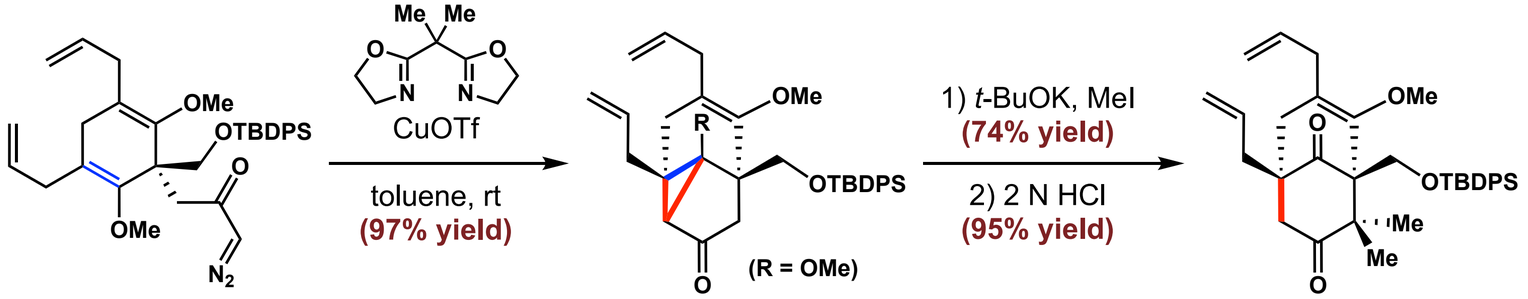

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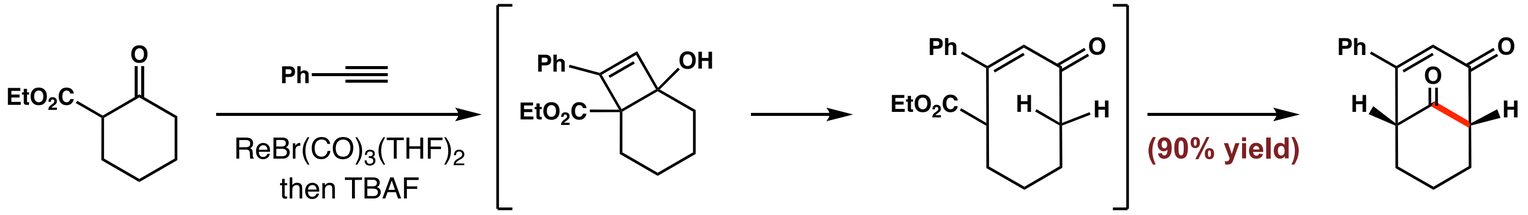

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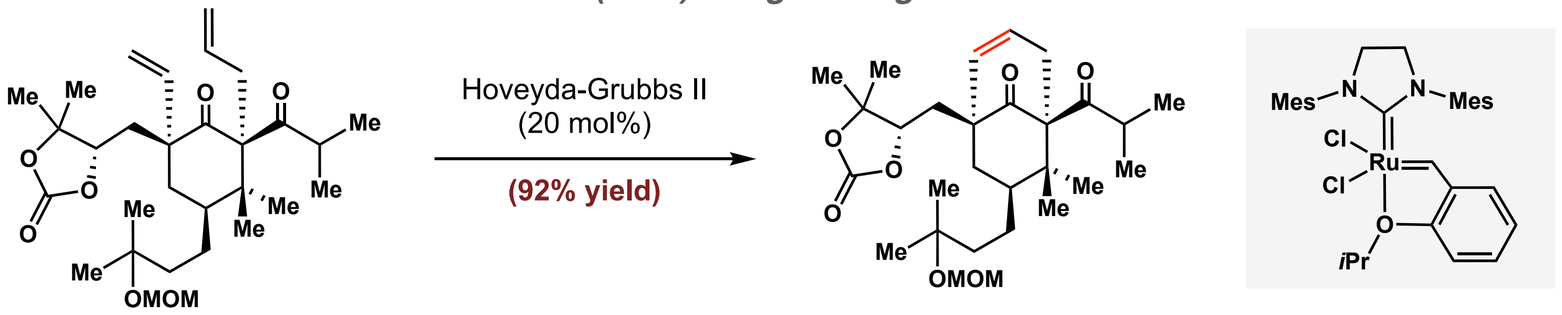
Shibasaki (2005): Ring-closing Metathesis



Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200.

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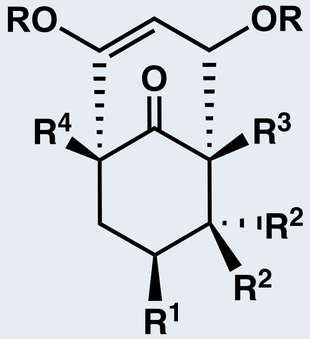
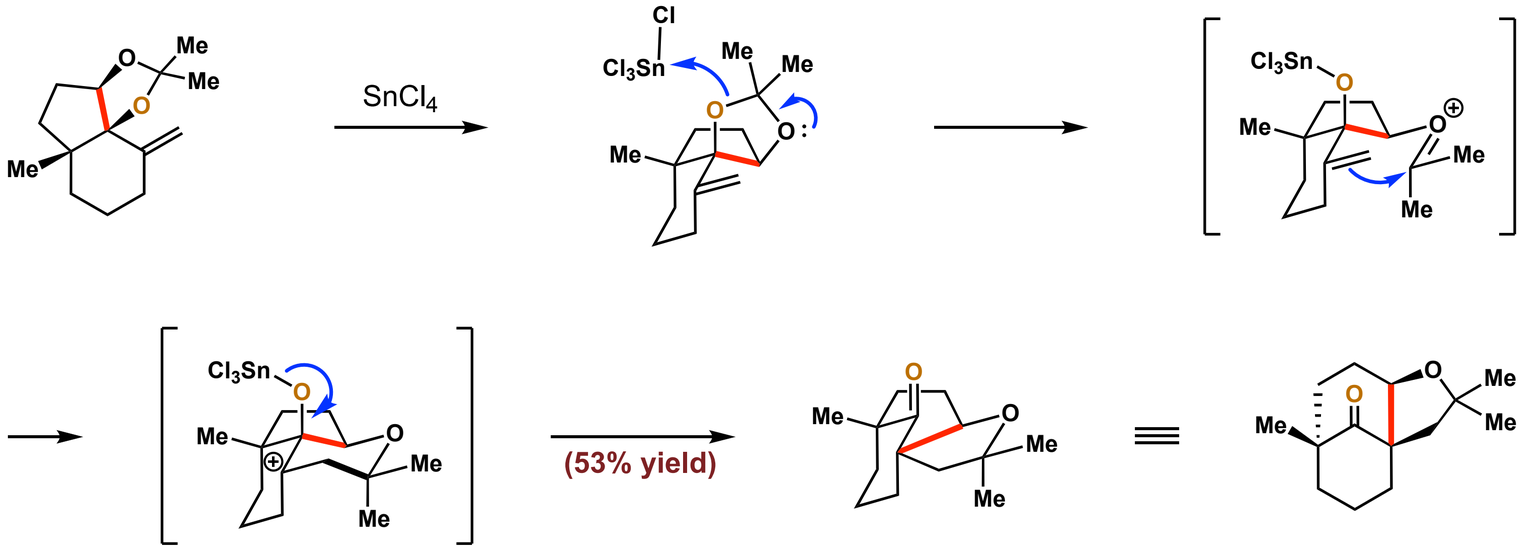


Barriault (2005): Tandem Prins/Semi-pinacol Rearrangement



Lavigne, R. M. A.; Riou, M.; Girardin, M.; Morency, L.; Barriault, L. *Org. Lett.* **2005**, *7*, 5921.

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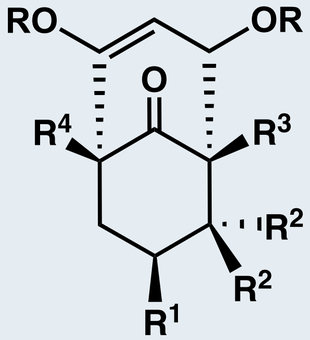

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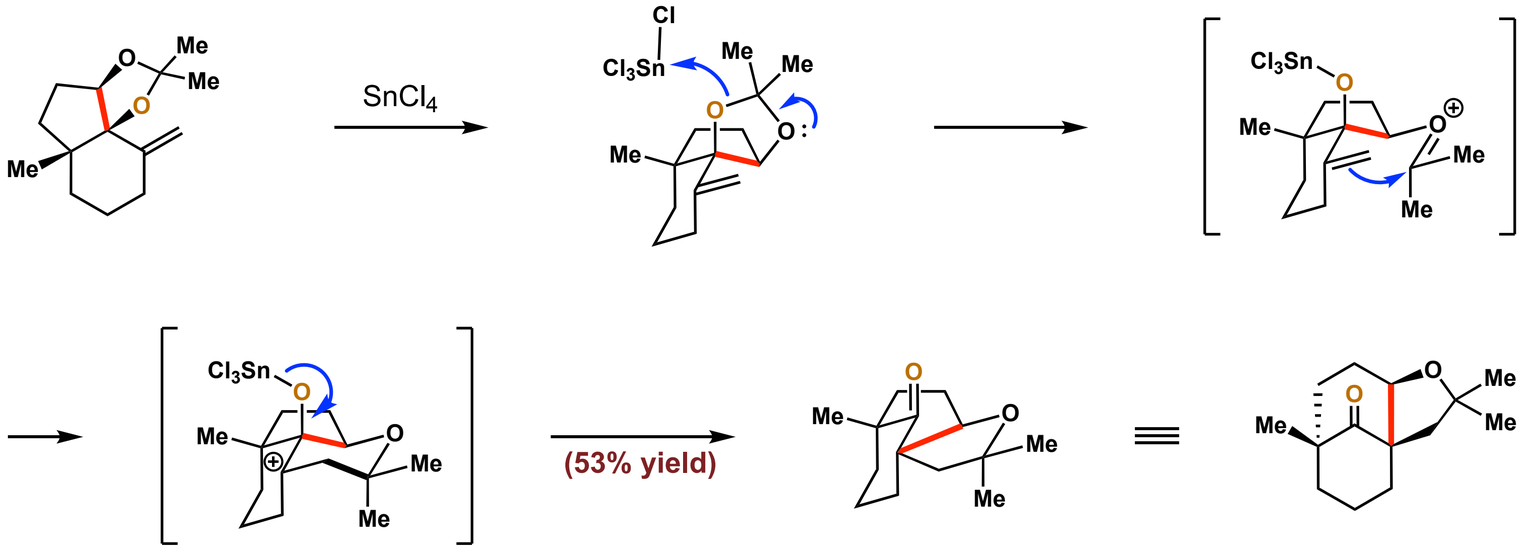
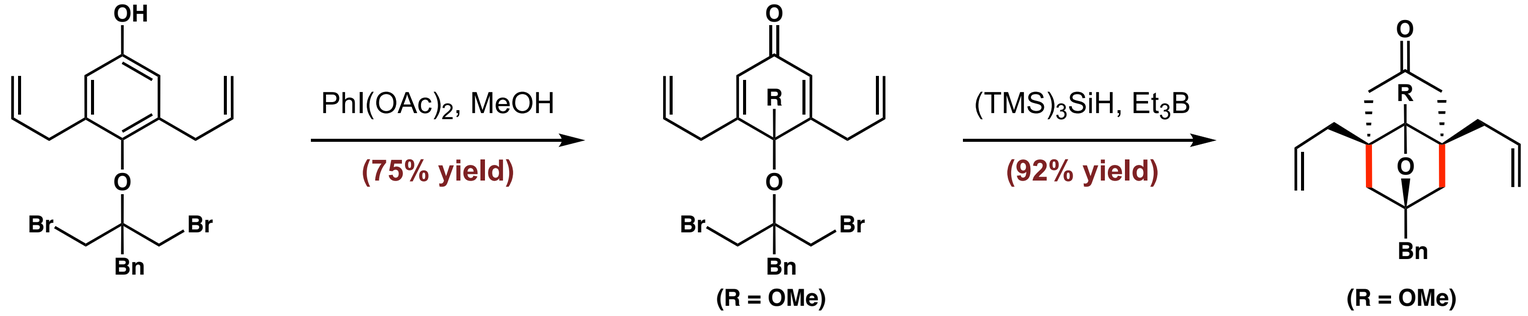


Lavigne, R. M. A.; Riou, M.; Girardin, M.; Morency, L.; Barriault, L. *Org. Lett.* **2005**, *7*, 5921.

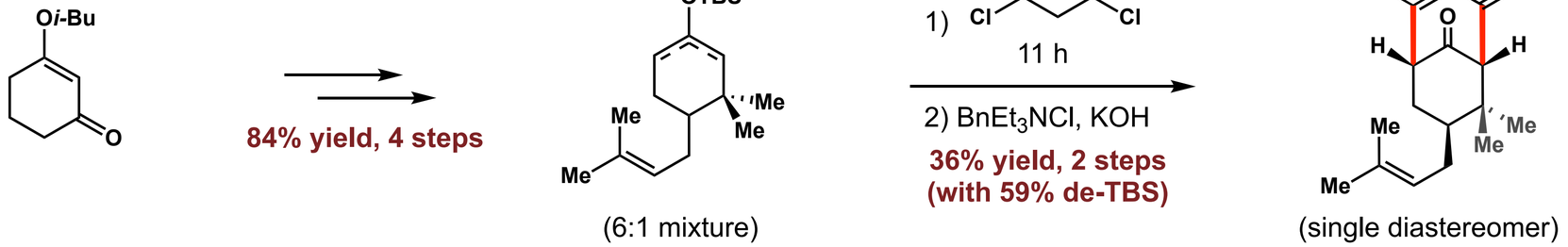
Njardarson (2011): Double Intramolecular Radical Cyclization

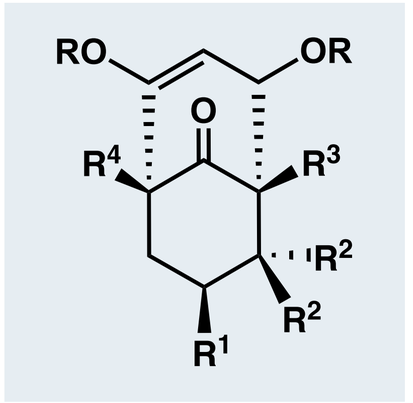


McGrath, N. A.; Binner, J. R.; Markopoulos, G.; Brichacek, M.; Njardarson, J. T. *Chem. Commun.* **2011**, *47*, 209.

Synthetic Strategies towards Bicyclo[3.3.1]nonane

Stoltz's Effenberger Cyclization Approach





Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943.

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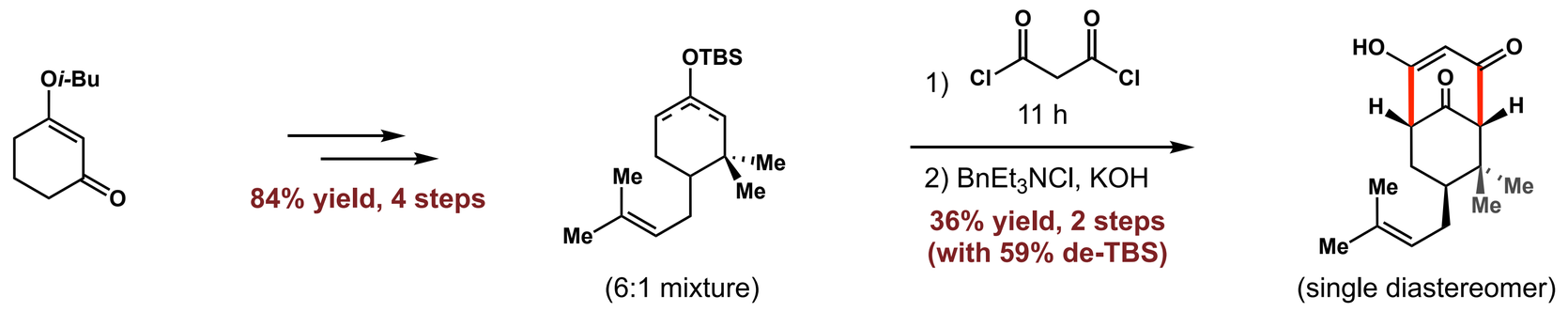
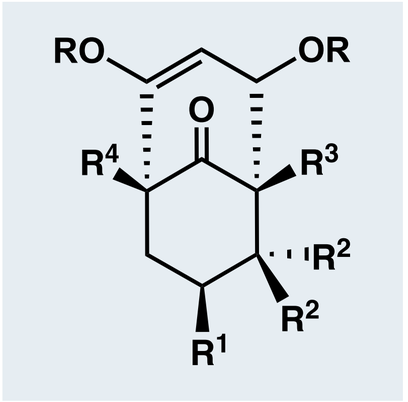
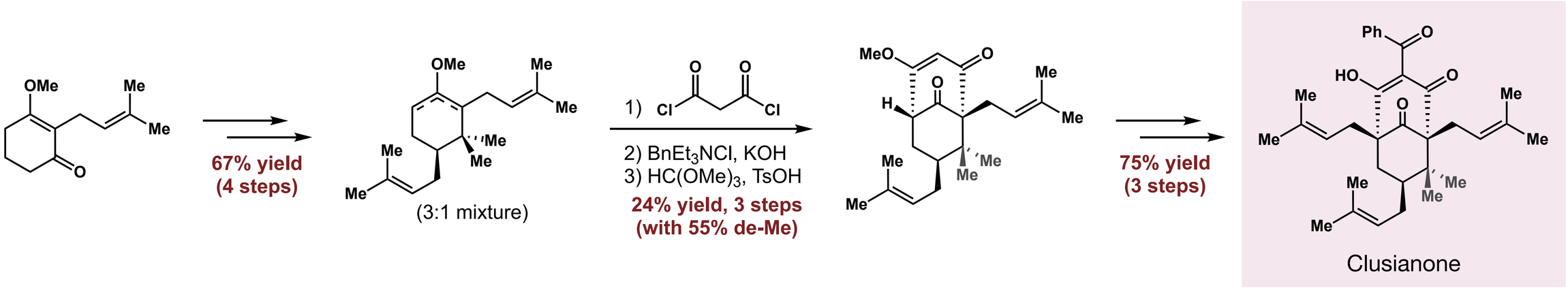




Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943.

Simpkins' Synthesis of (±)-Clusianone



Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett.* **2006**, *8*, 5283.

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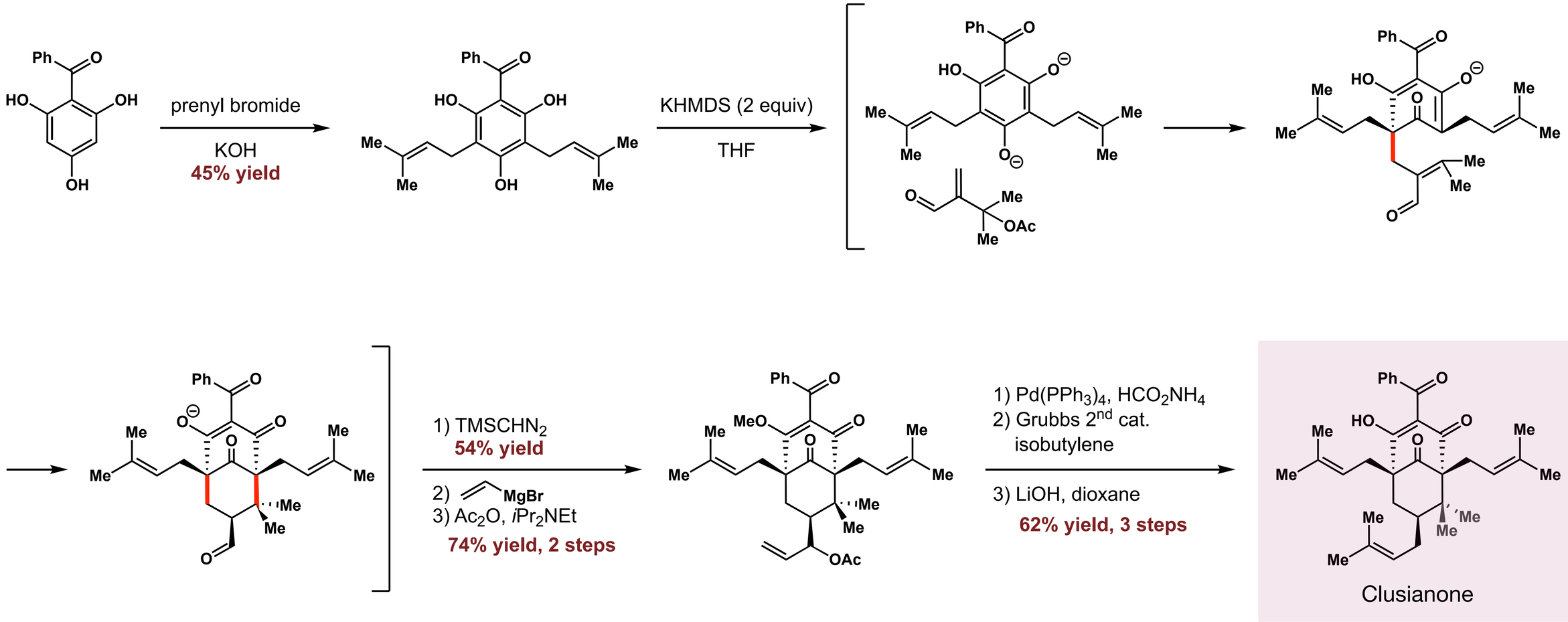
■ Porco's Biomimetic Dearomatization/Annulation Strategy



Qi, J.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 12682.

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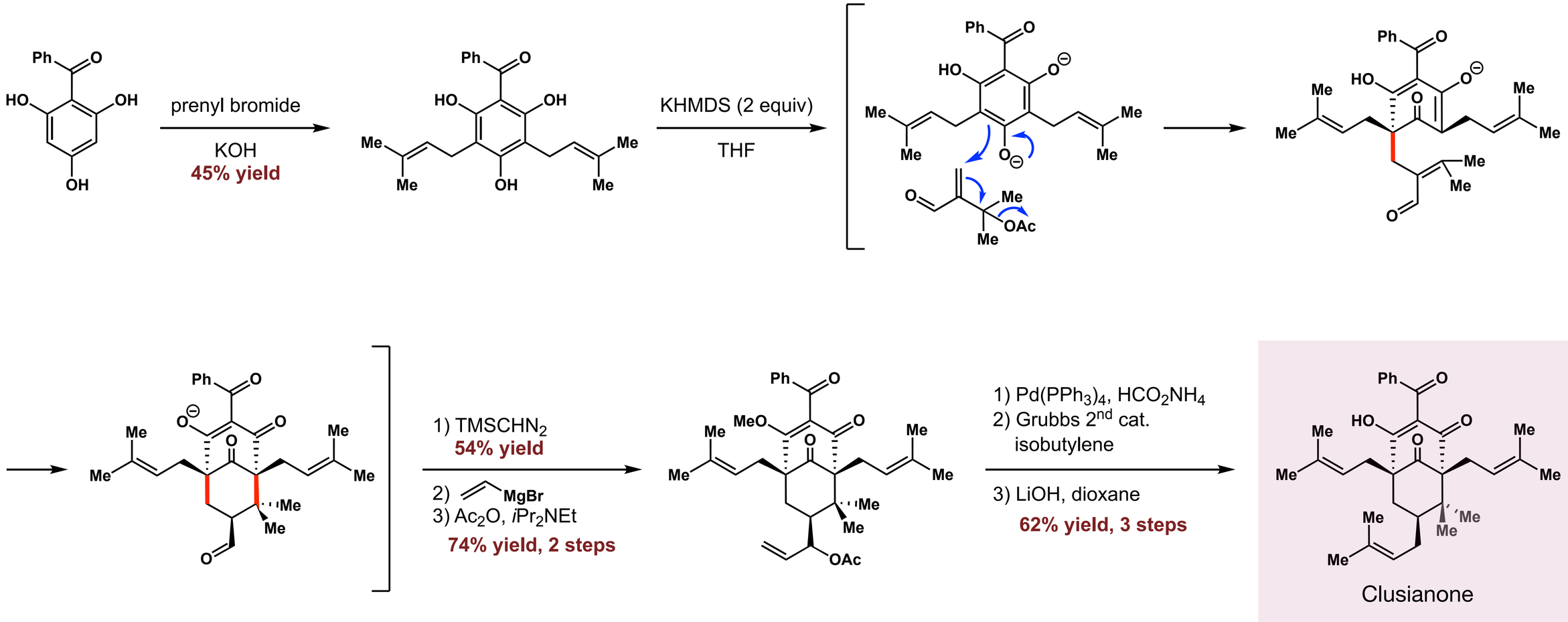

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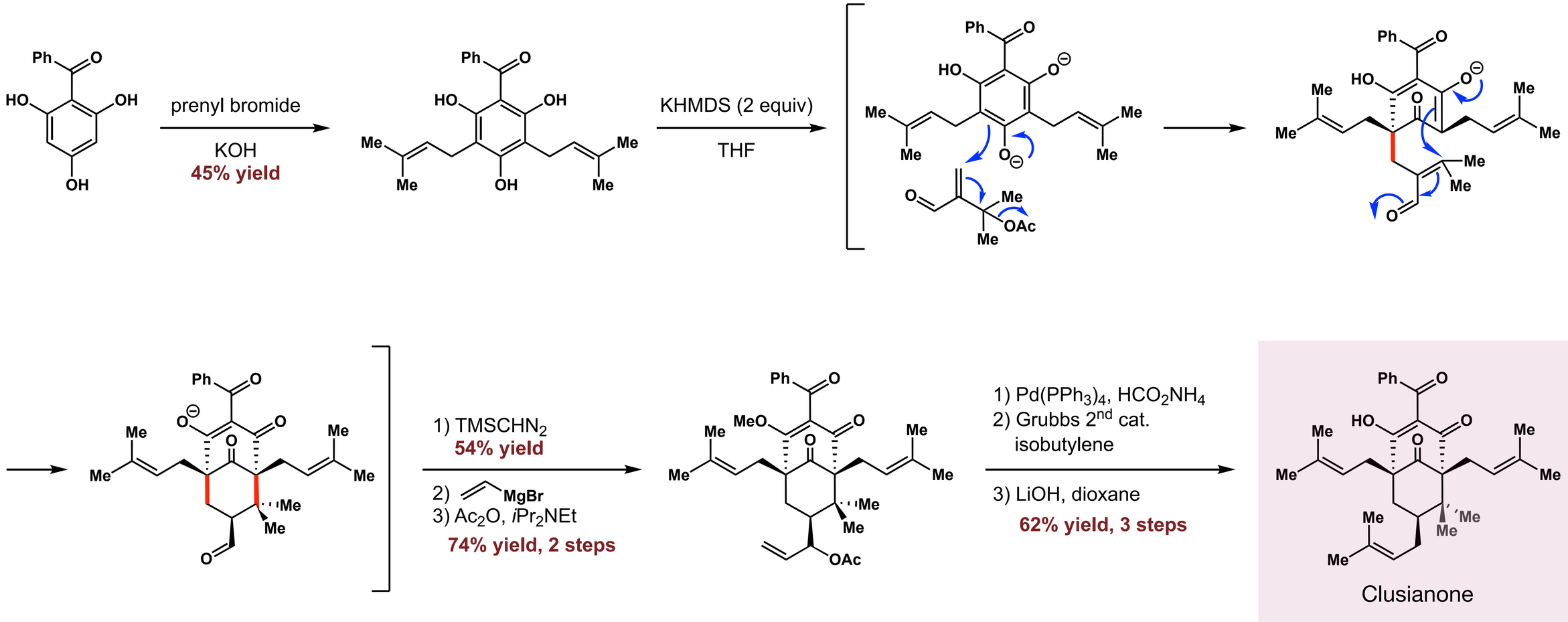

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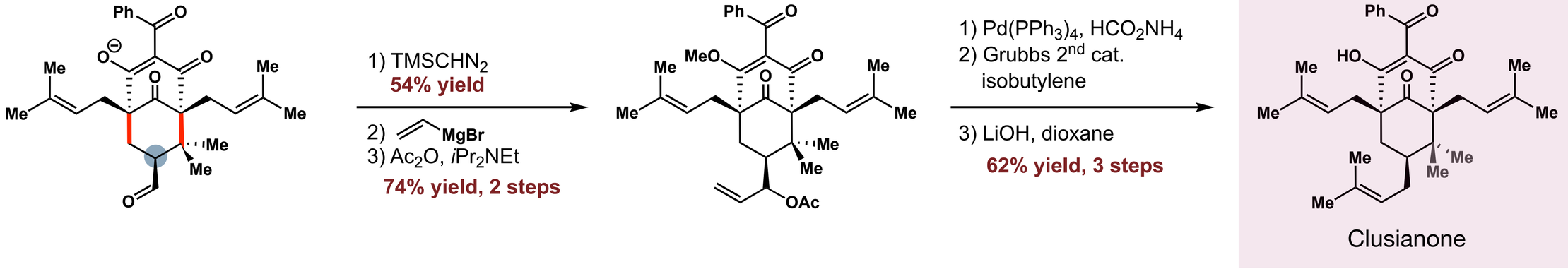

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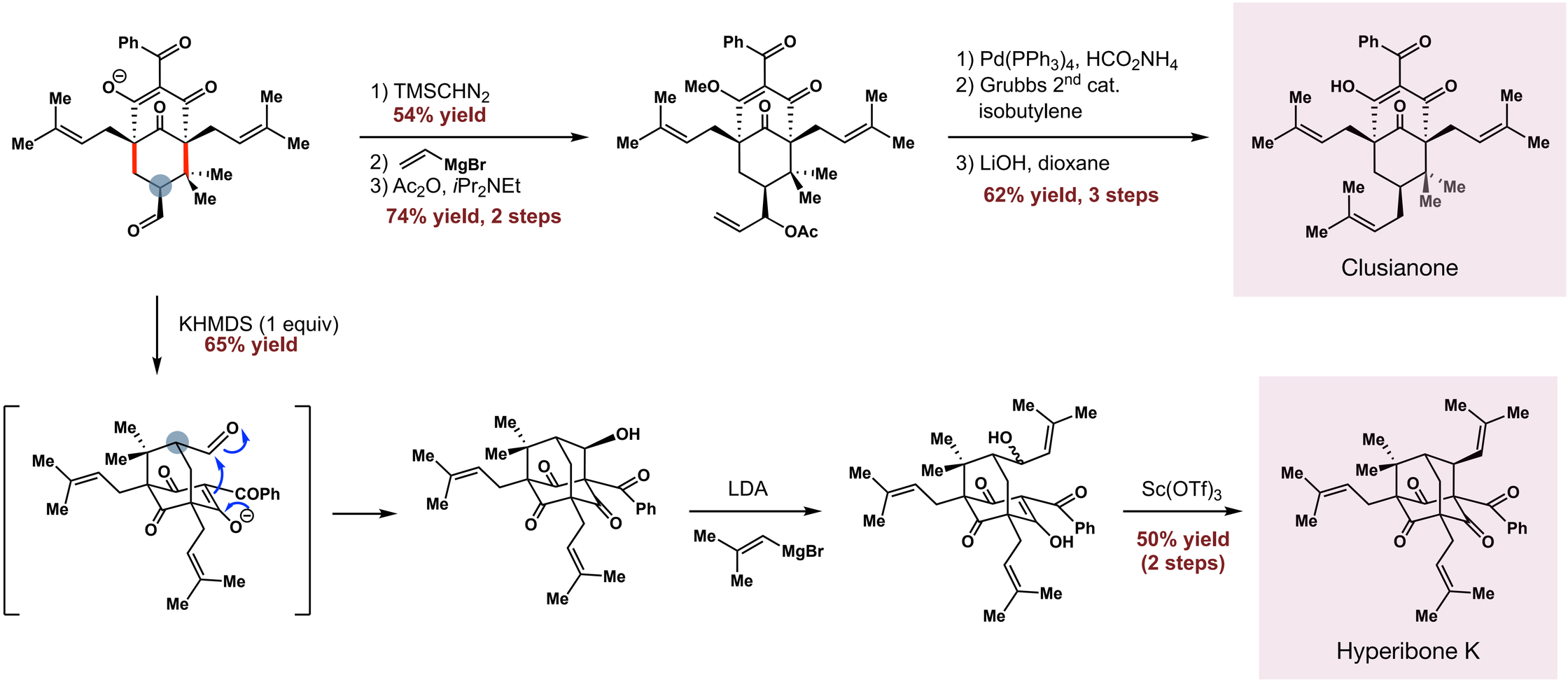

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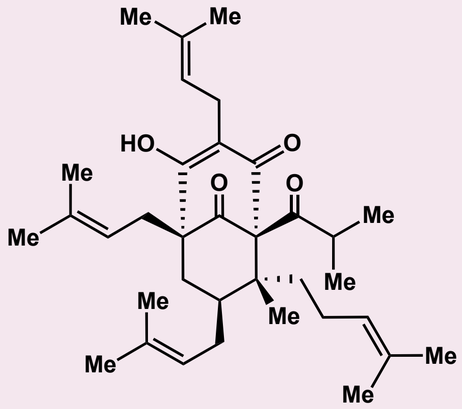
Total Synthesis of Hyperforin: A Quest of Synthetic Efficiency



Hyperforin

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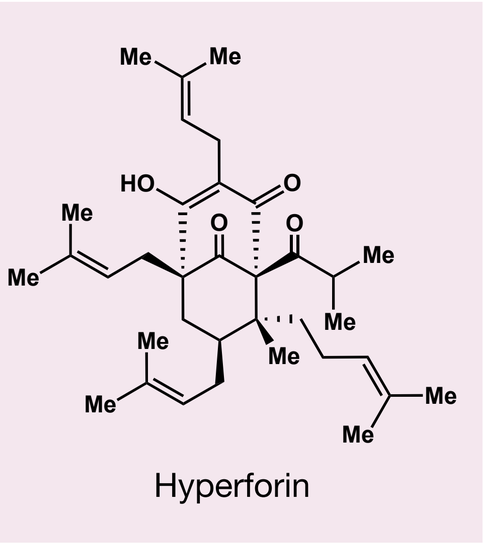

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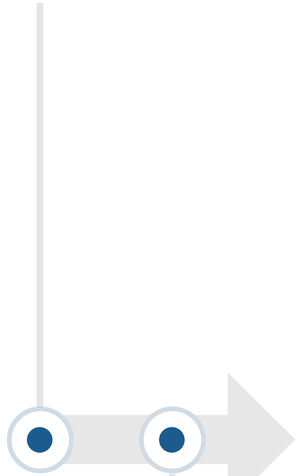
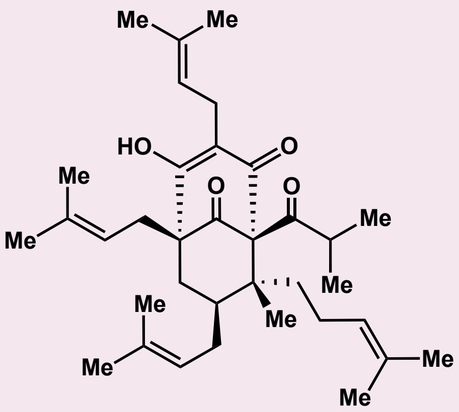


1975: Structure Elucidation



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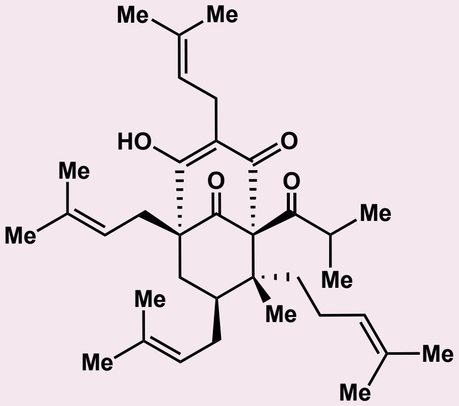

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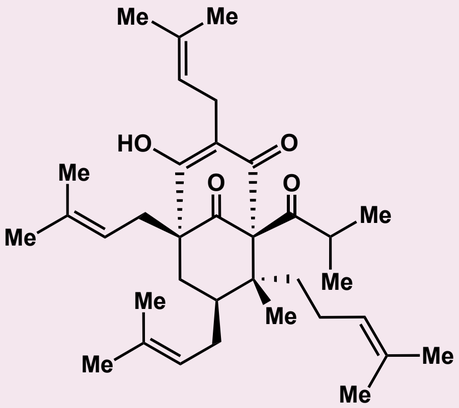

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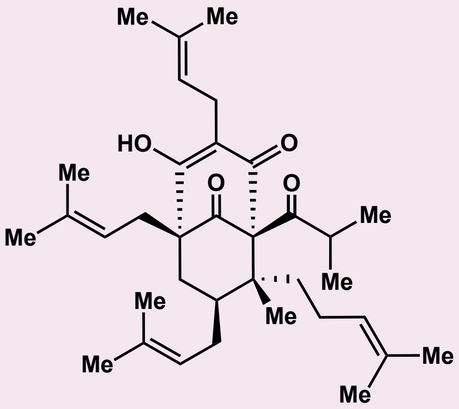

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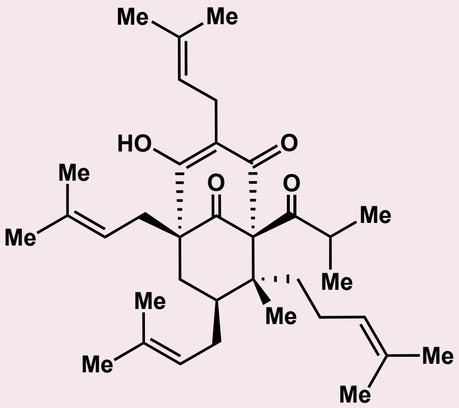

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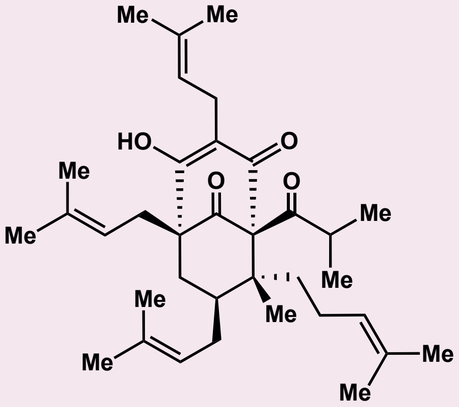

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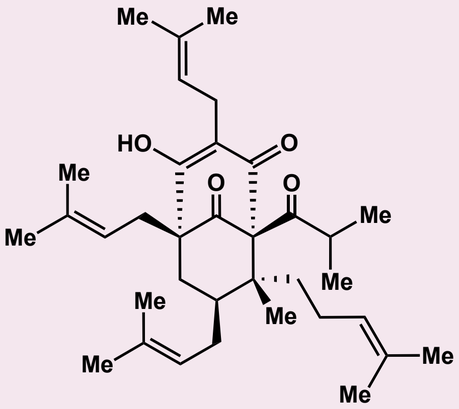

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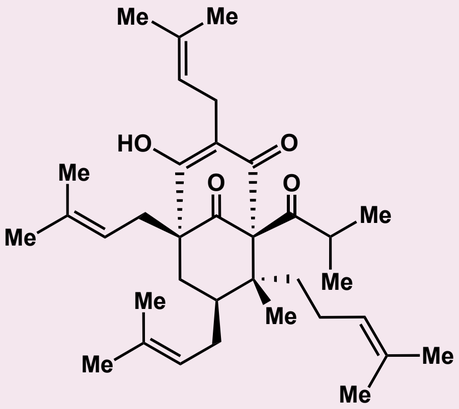
2014: L. Barriault (**17 steps LLS**)

1975: Structure Elucidation

2013: M. Nakada (**35 steps LLS**)



Hyperforin

Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103.
Uwamori, M.; Nakada, M. *Tetrahedron Lett.* **2013**, *54*, 2022.
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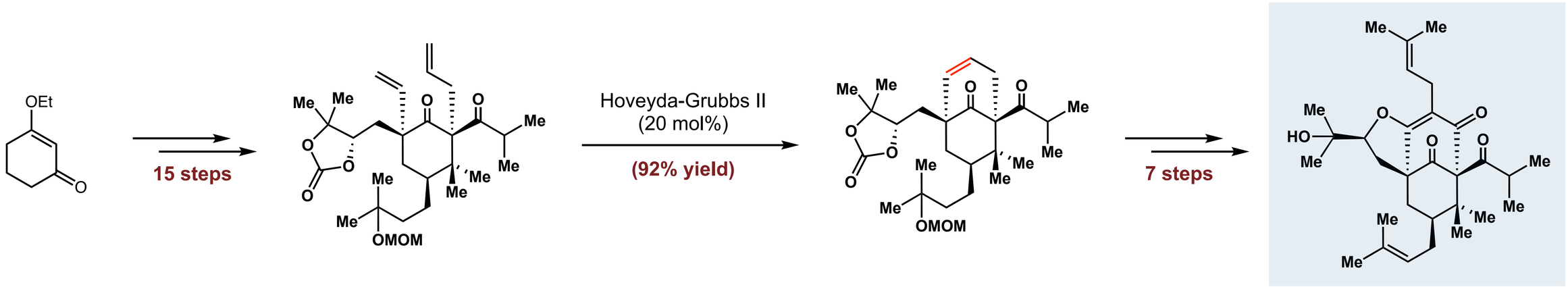
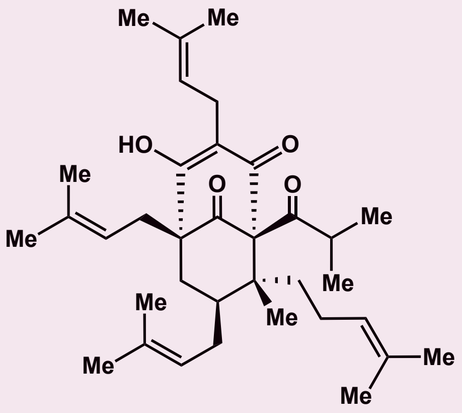
Li, Y.; Hong, B.; Franzoni, I.; Wang, M.; Guan, W.; Jia, H.; Li, H. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116136.

Total Synthesis of ent-Hyperforin (Shibasaki)

Shibasaki (2005): Total Synthesis of Garsubellin A



Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200.



Hyperforin

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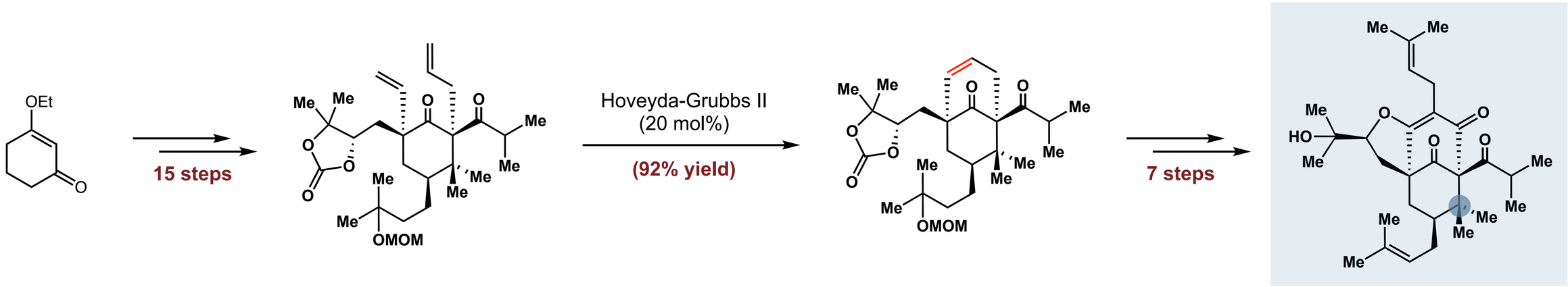
Shibasaki (2005): Total Synthesis of Garsubellin A



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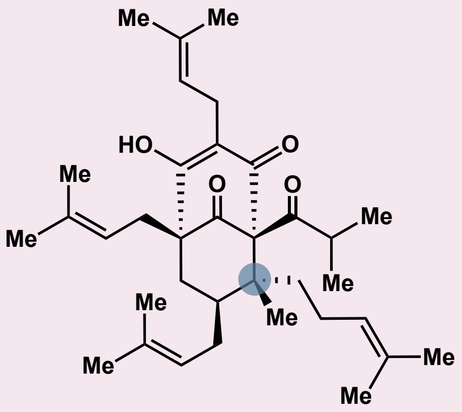

Hyperforin

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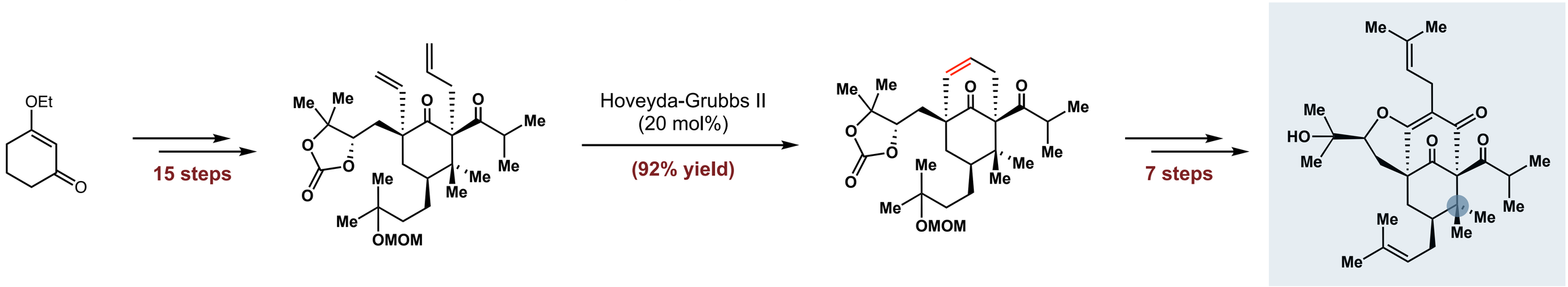
Shibasaki (2005): Total Synthesis of Garsubellin A



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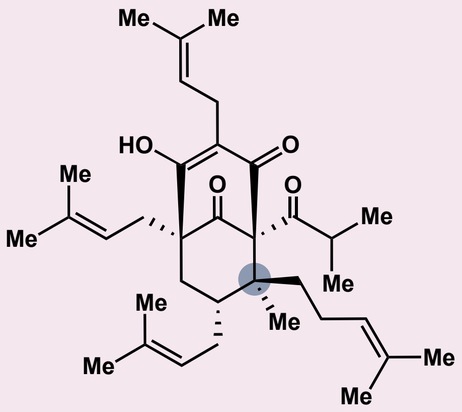

ent-Hyperforin

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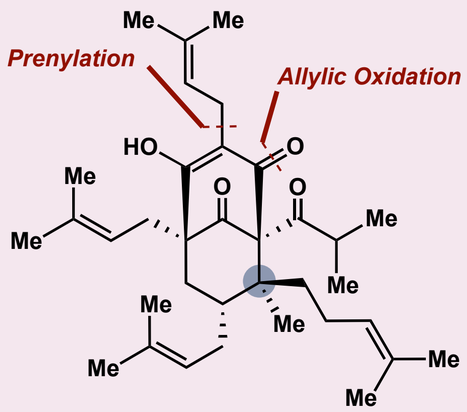

ent-Hyperforin

Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2010**, *66*, 6569.
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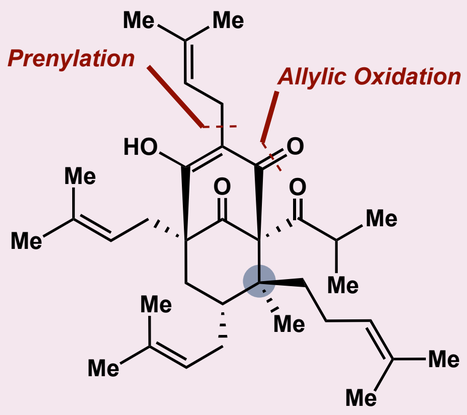

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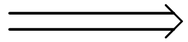

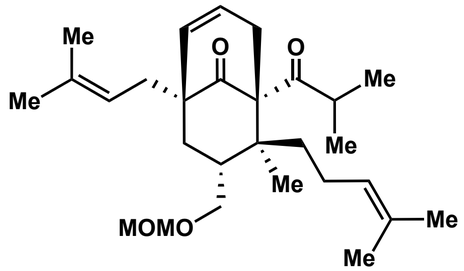

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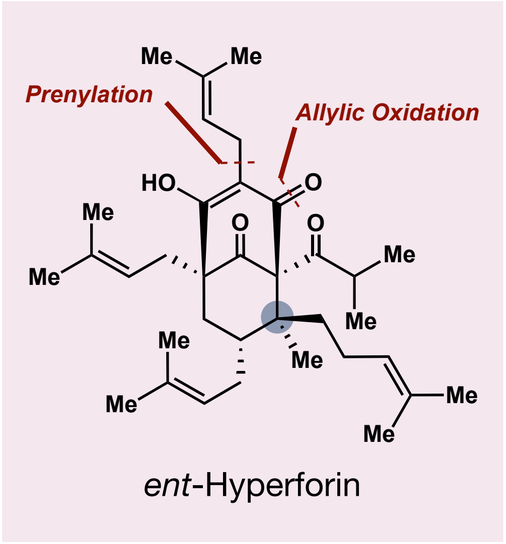

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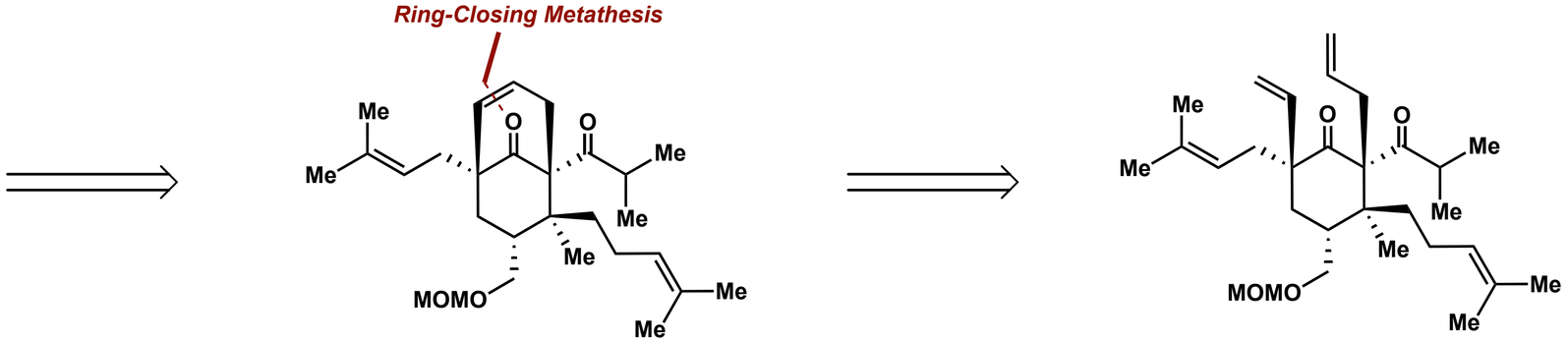

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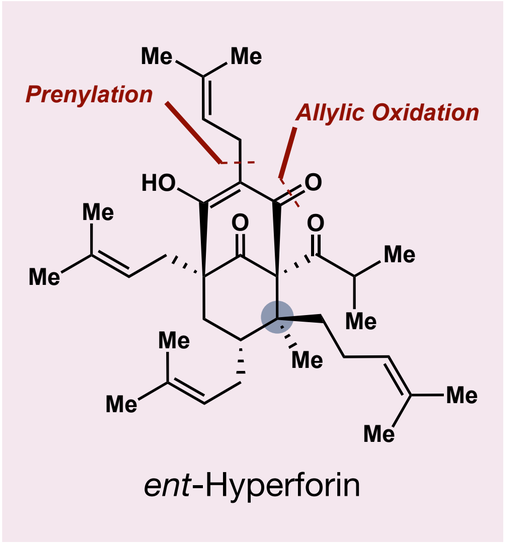

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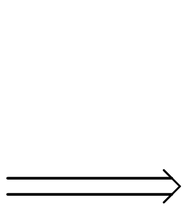

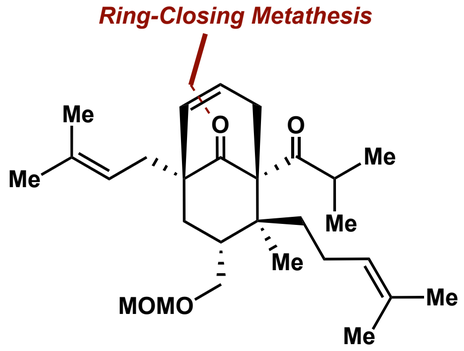

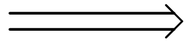

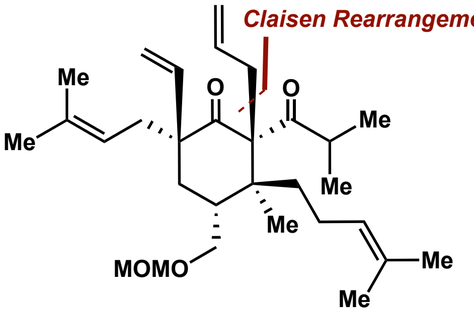

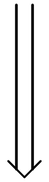

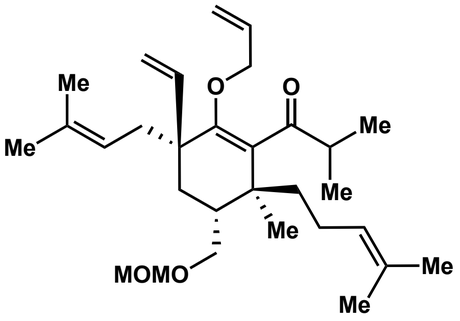

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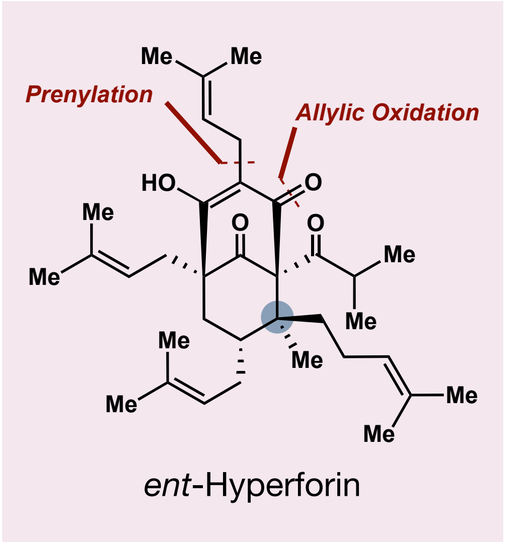
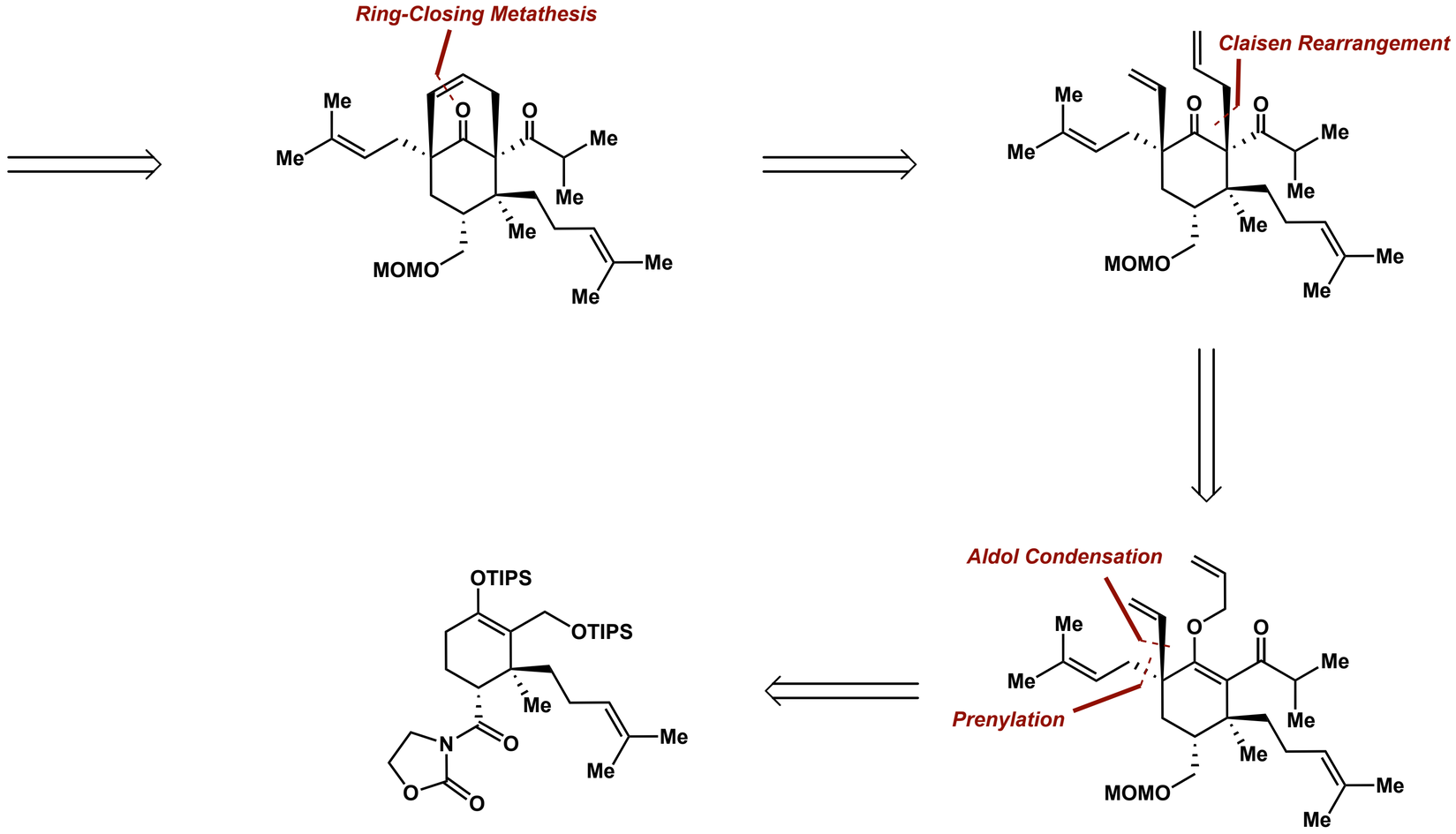
Total Synthesis of ent-Hyperforin (Shibasaki)



ent-Hyperforin



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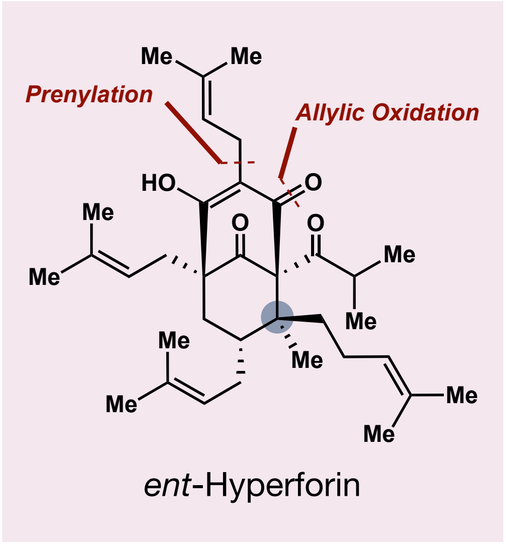

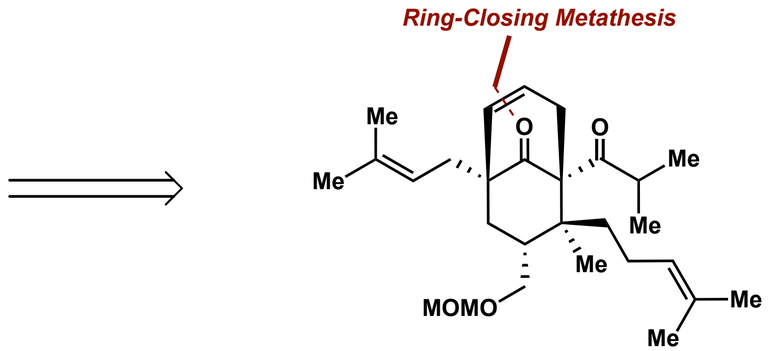

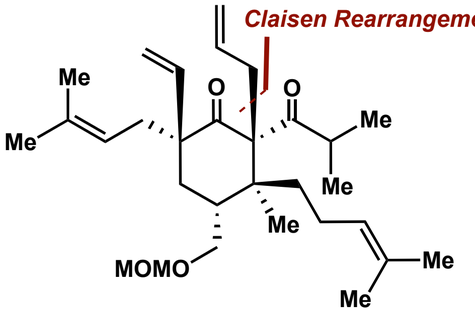

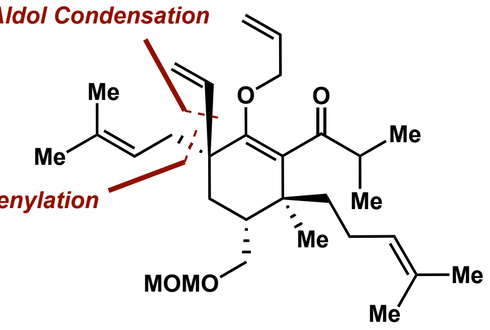

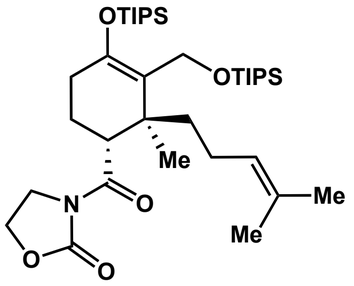

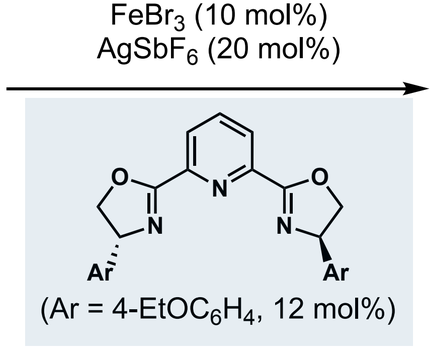

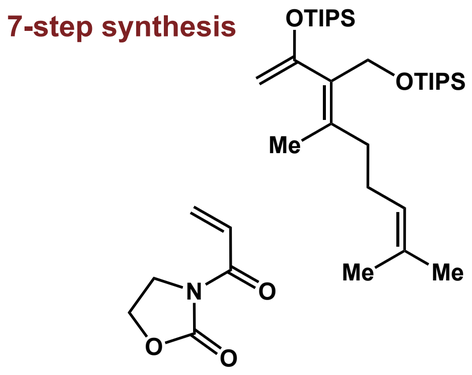

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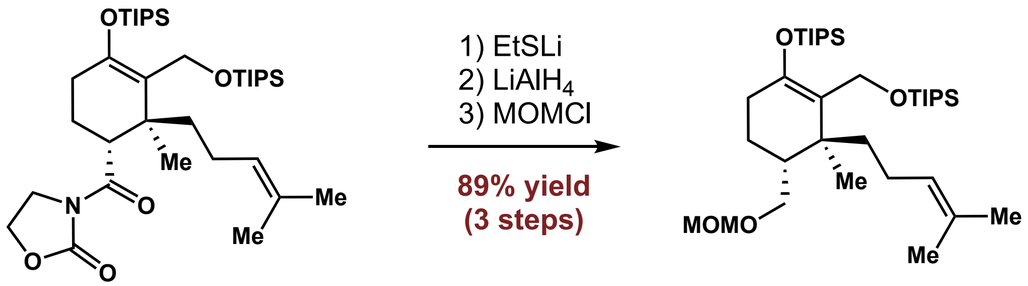
Total Synthesis of ent-Hyperforin (Shibasaki)



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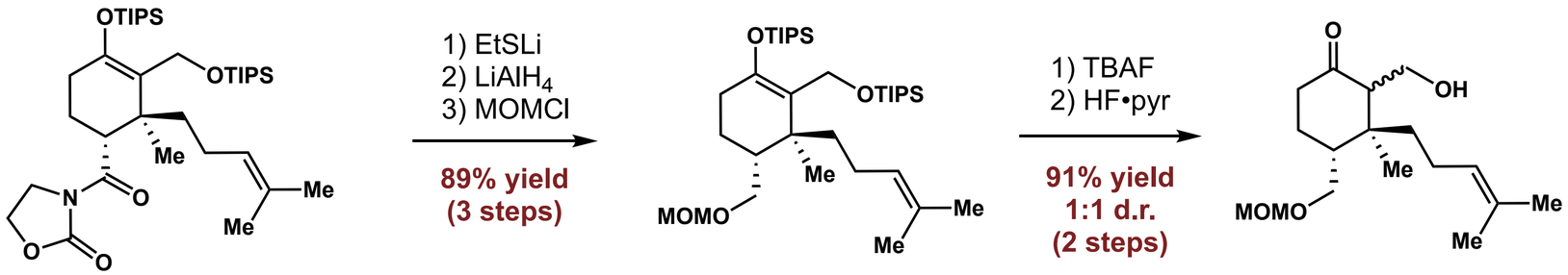

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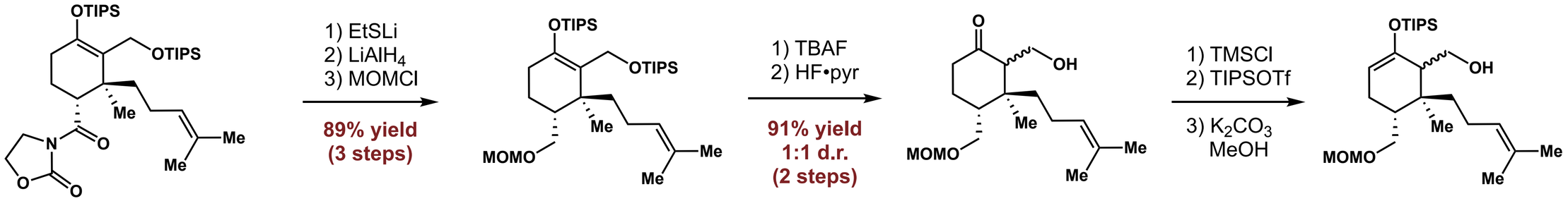

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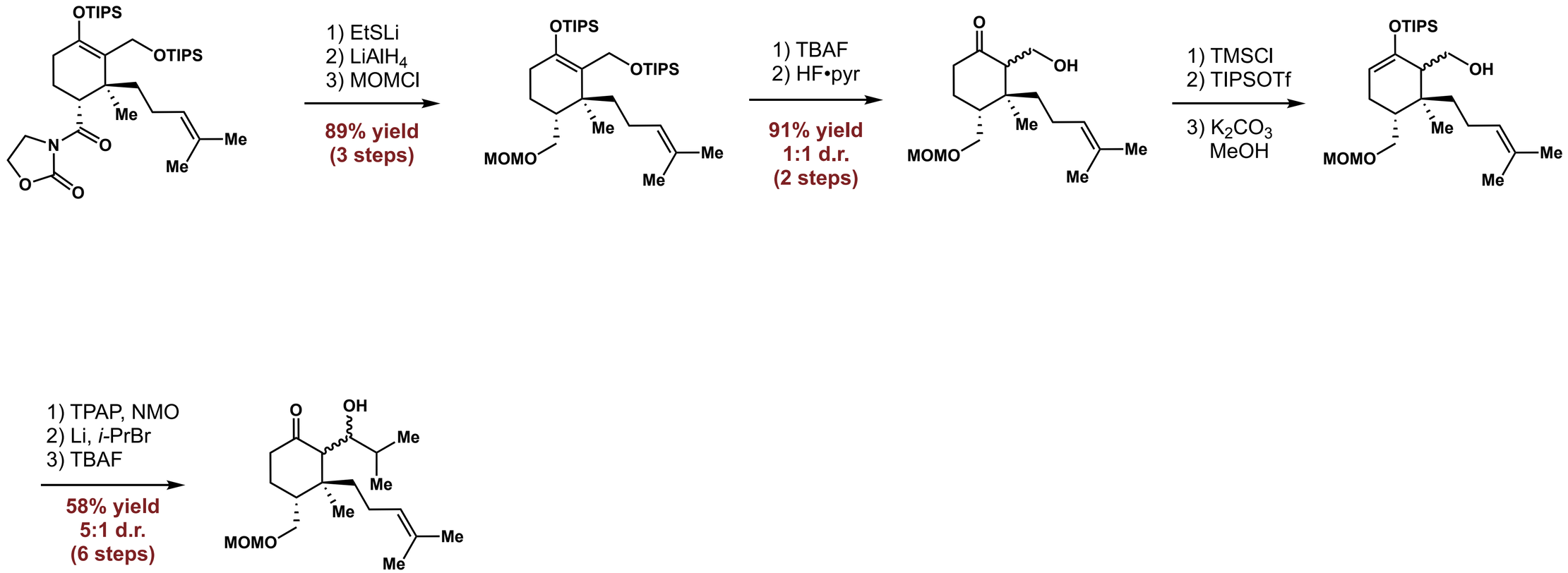

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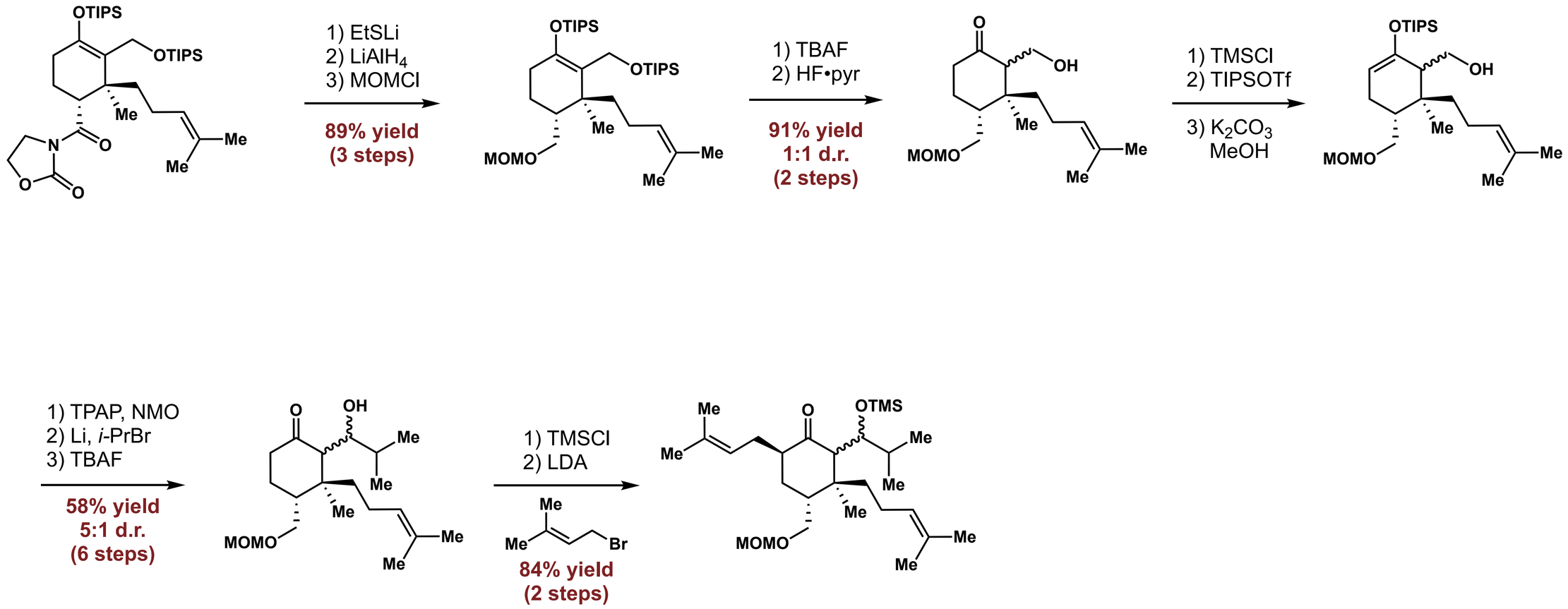

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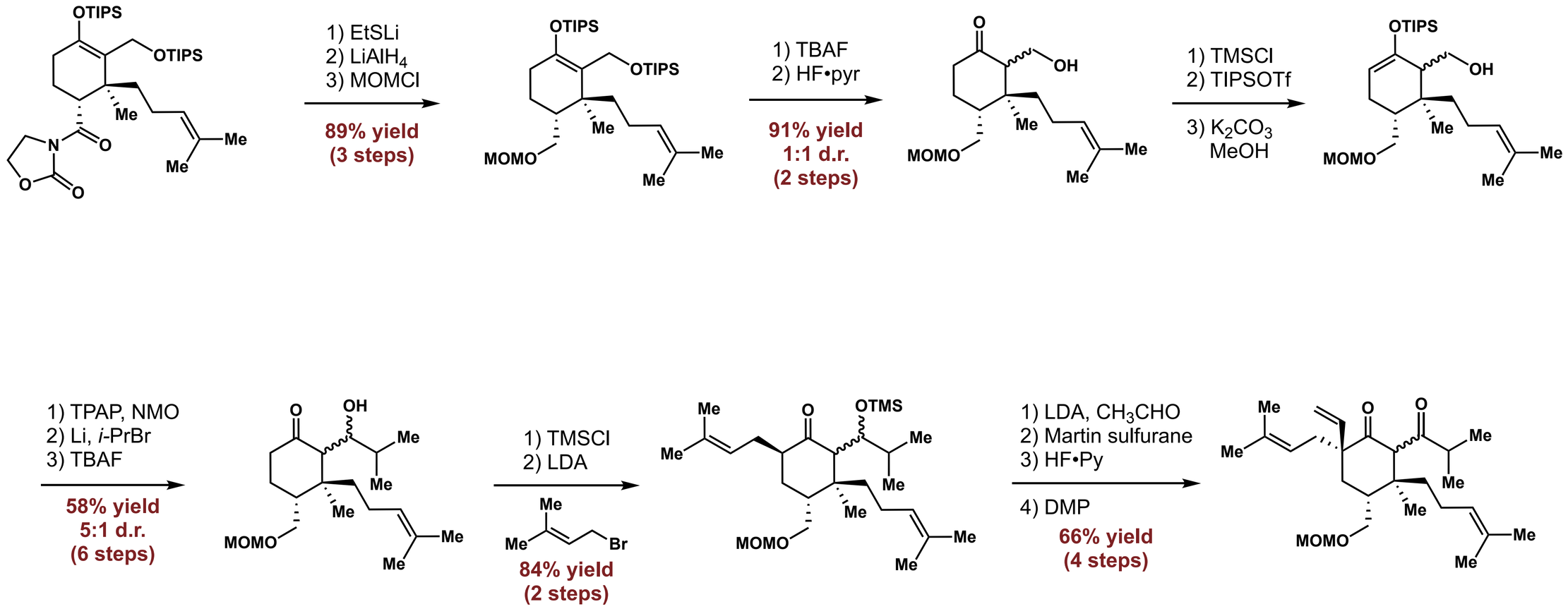

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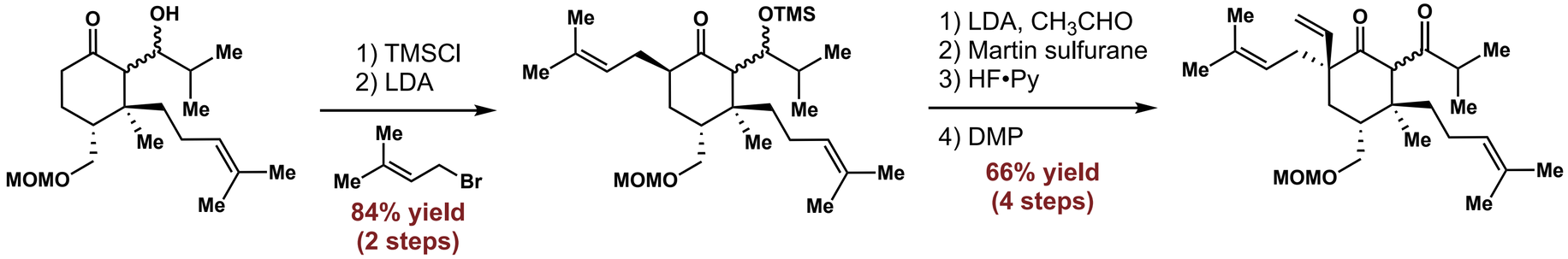

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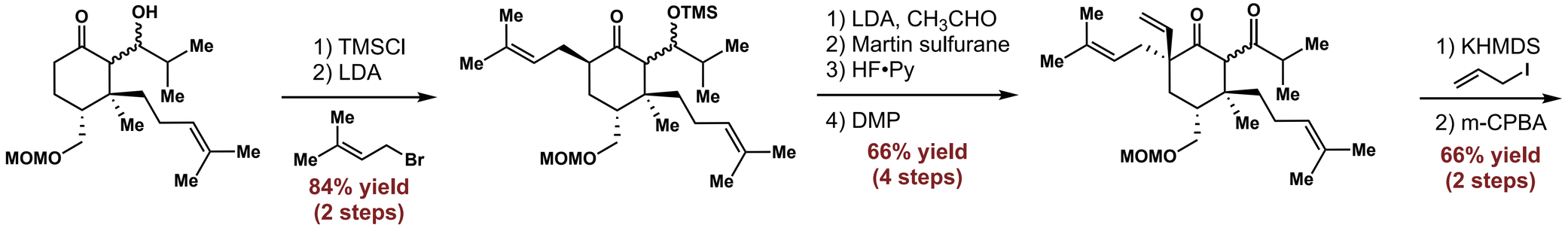

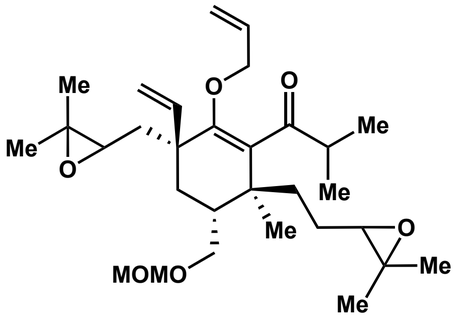

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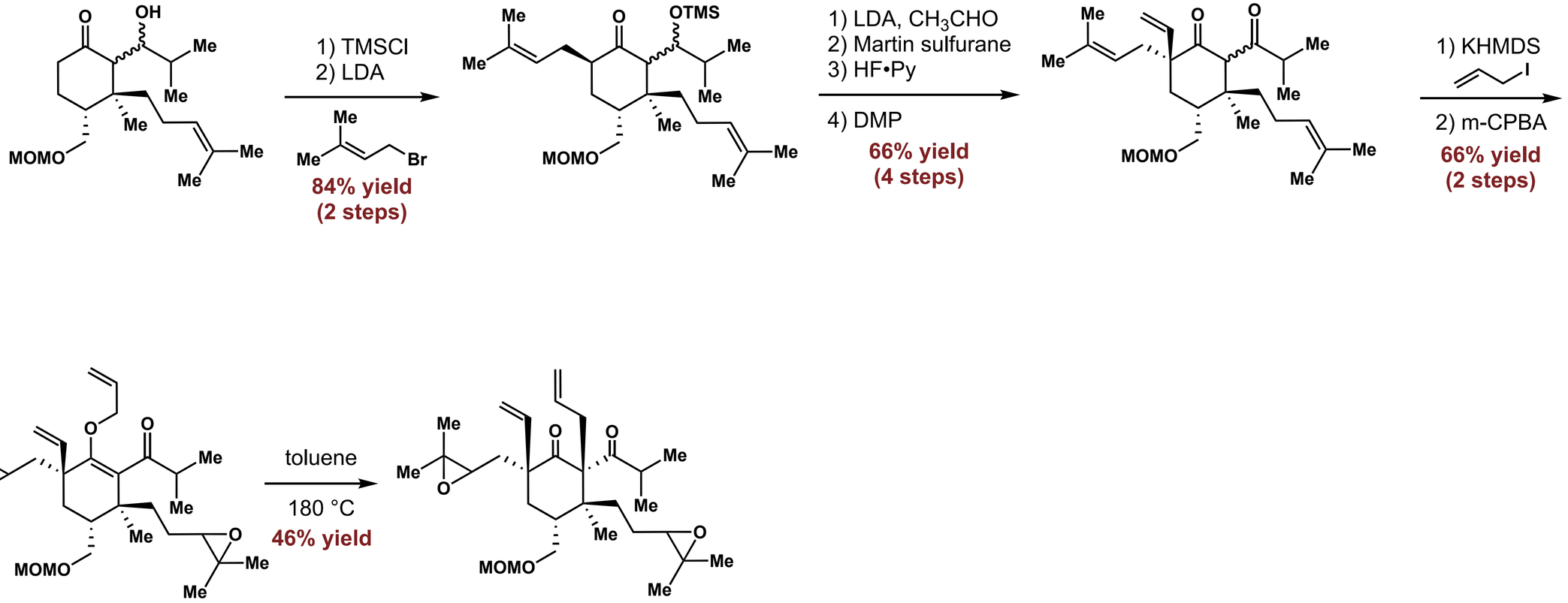

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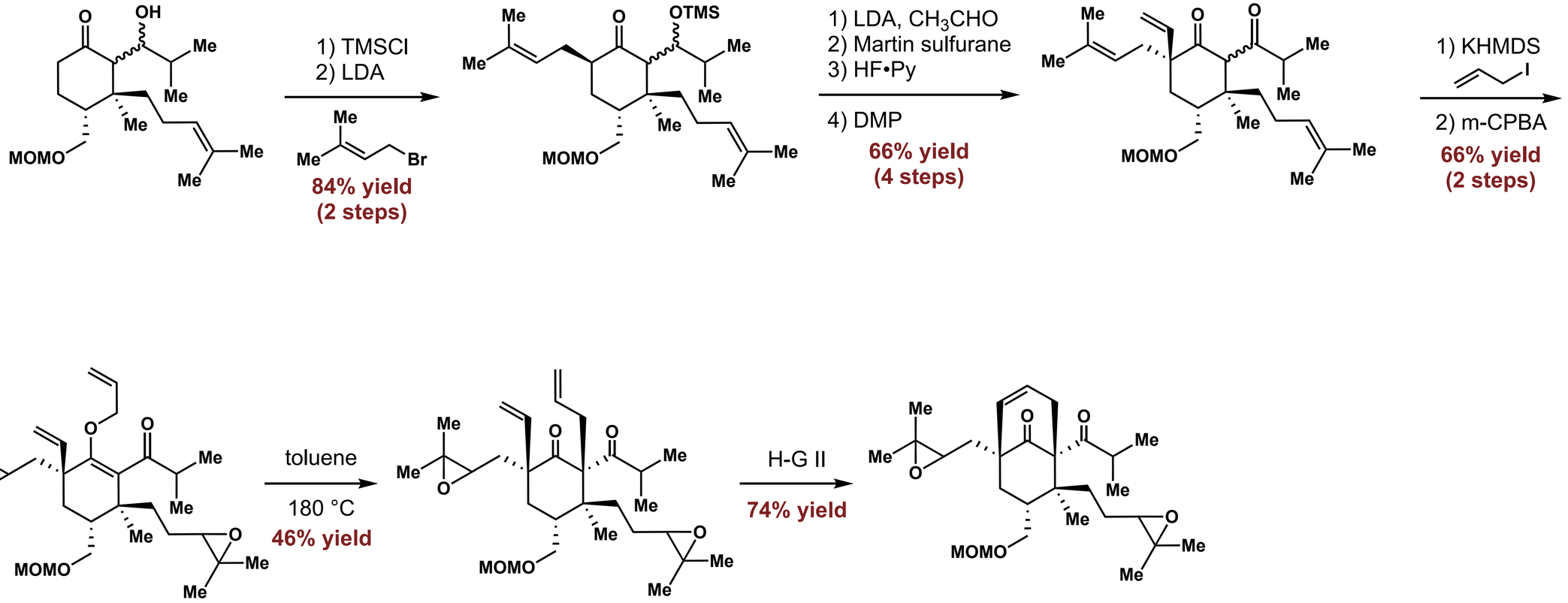

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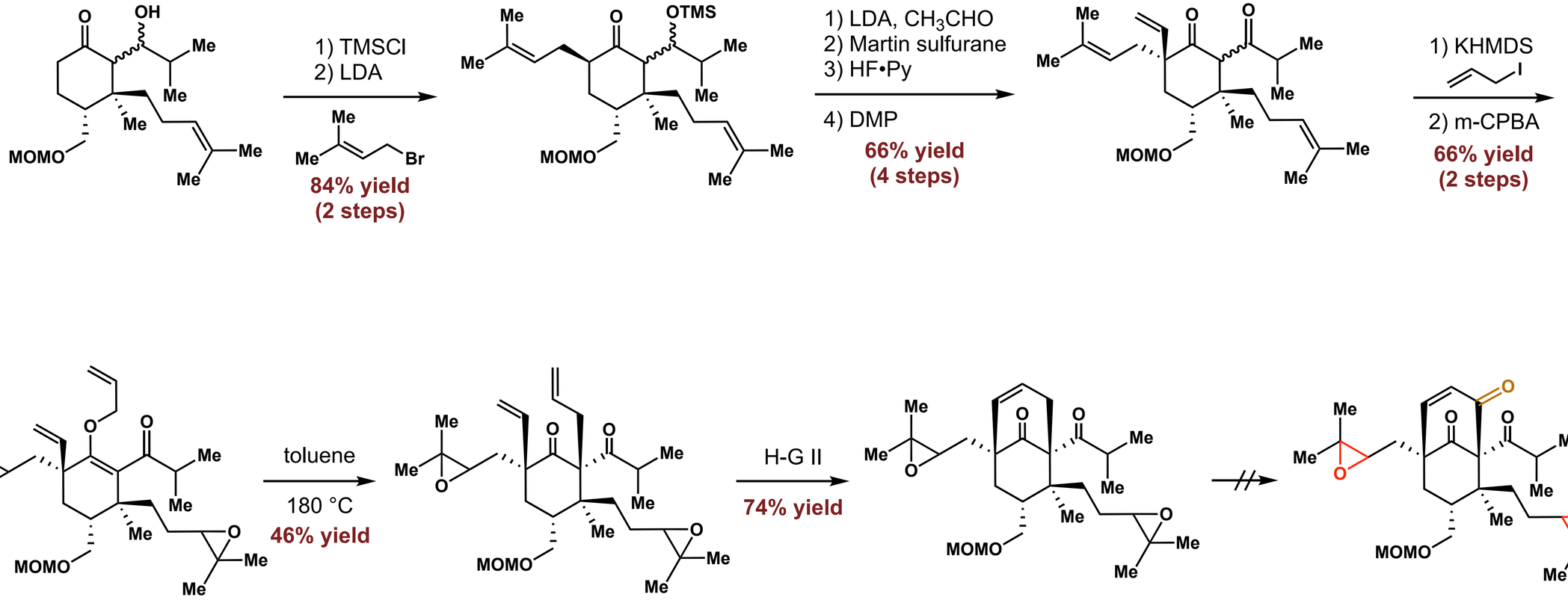

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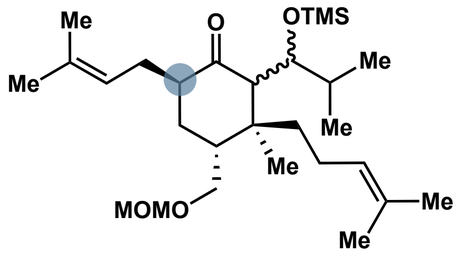

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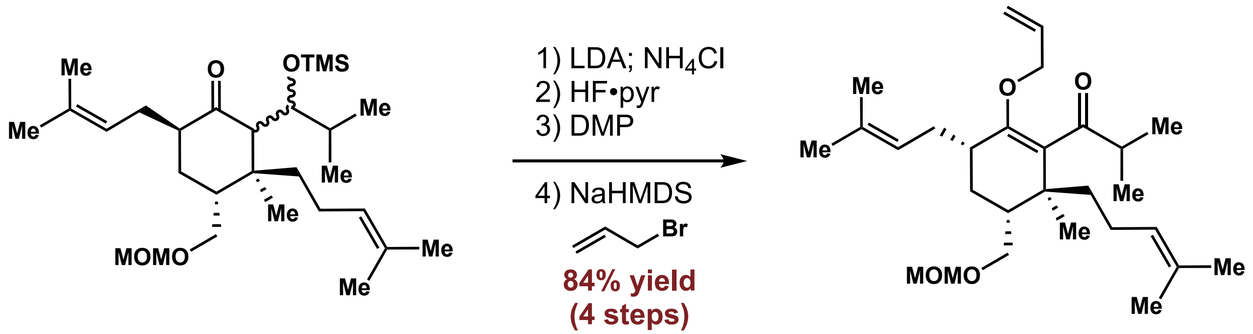

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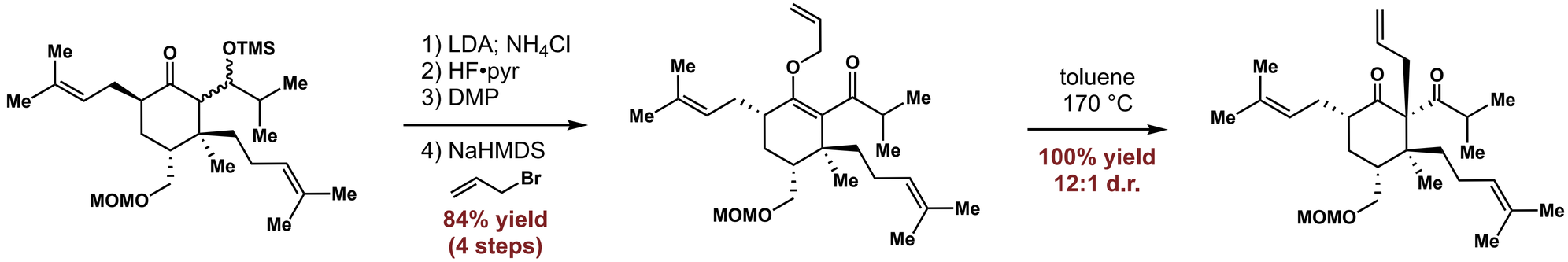

Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2010**, *66*, 6569.
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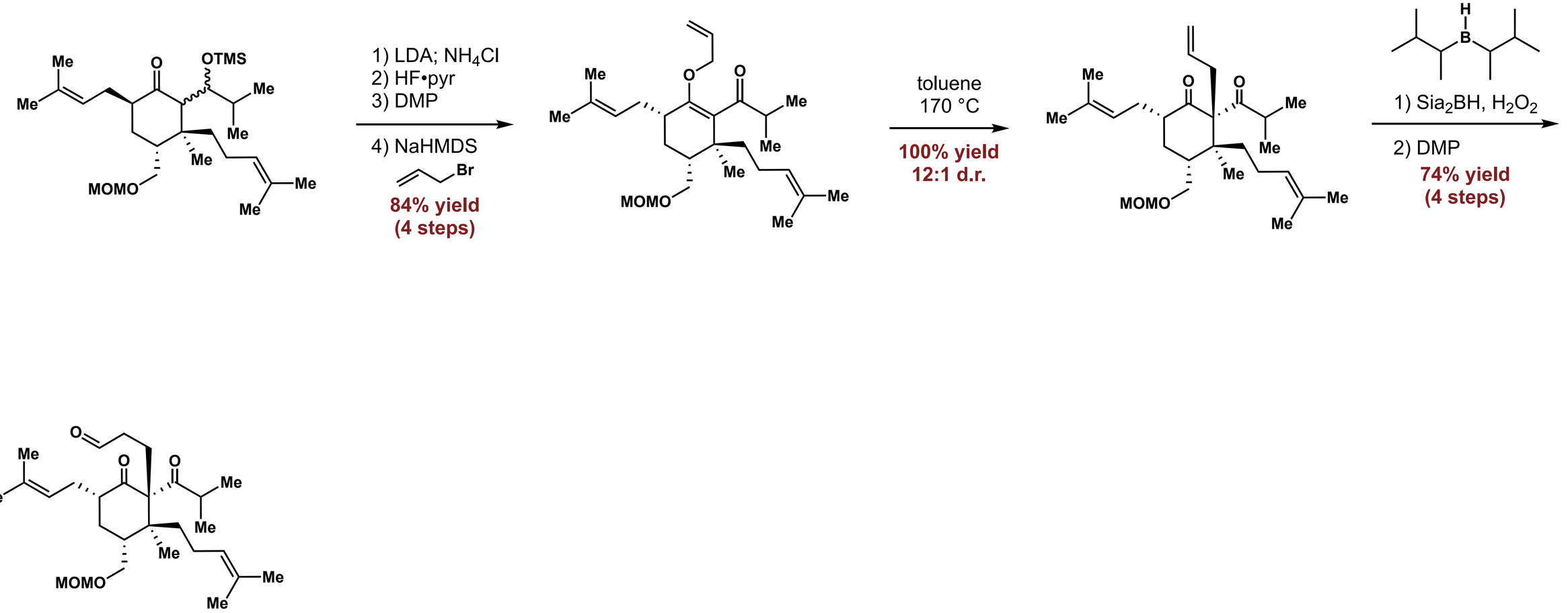

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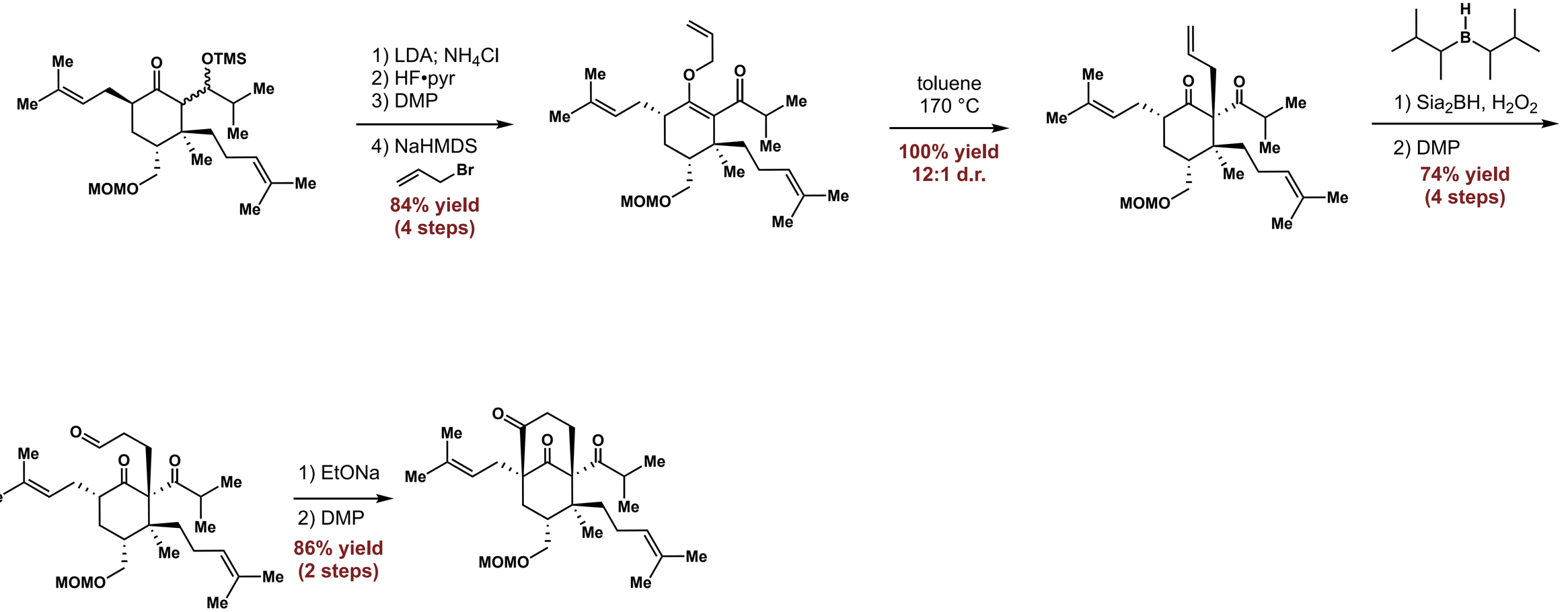

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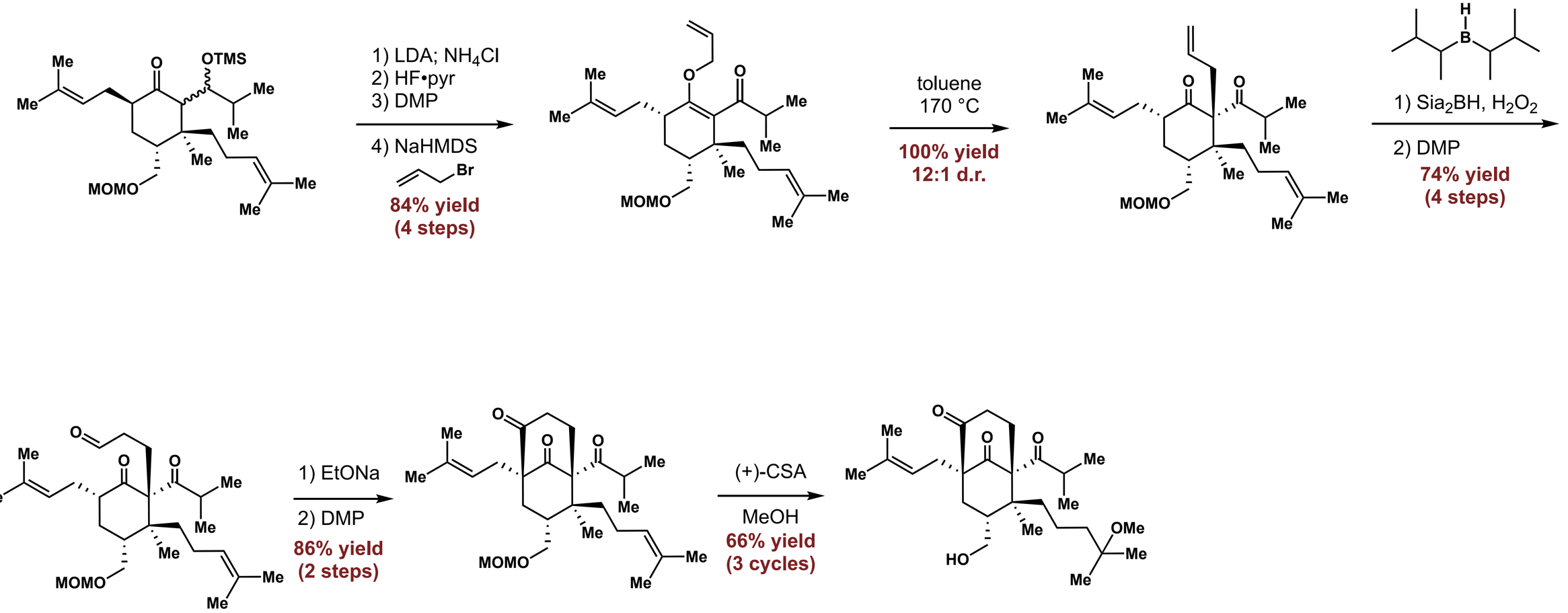

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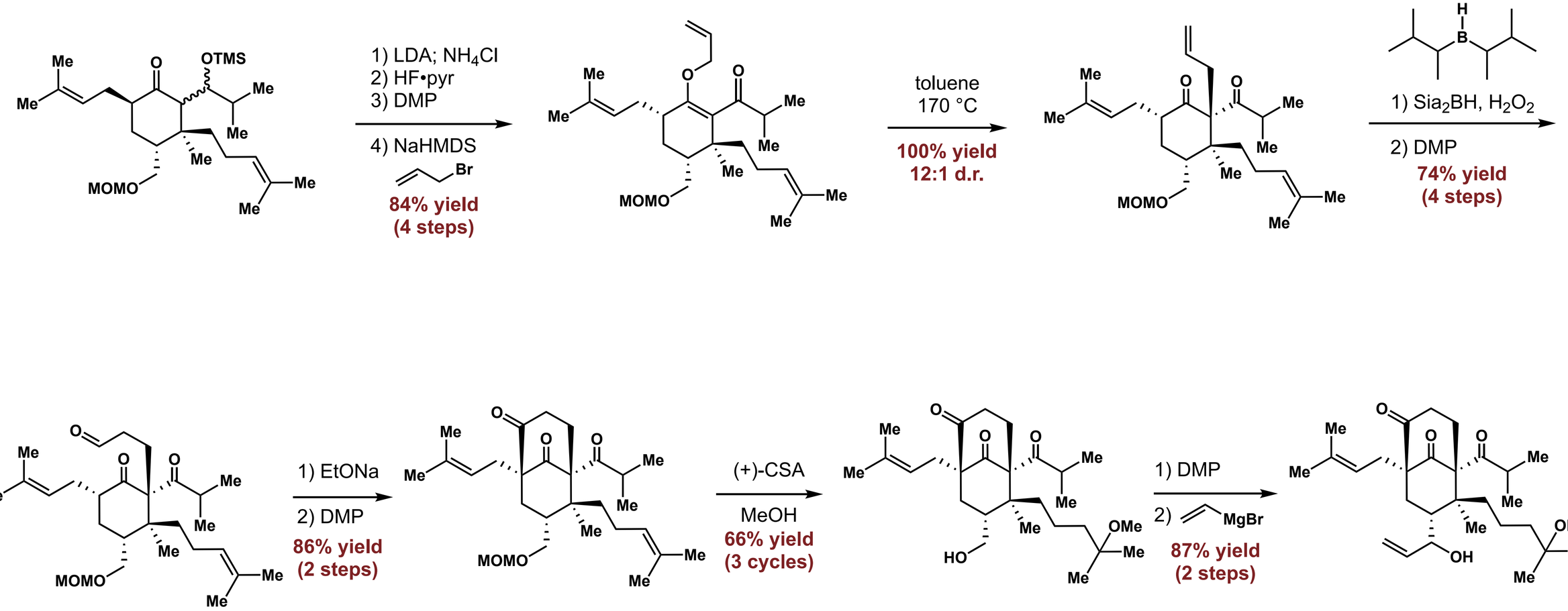

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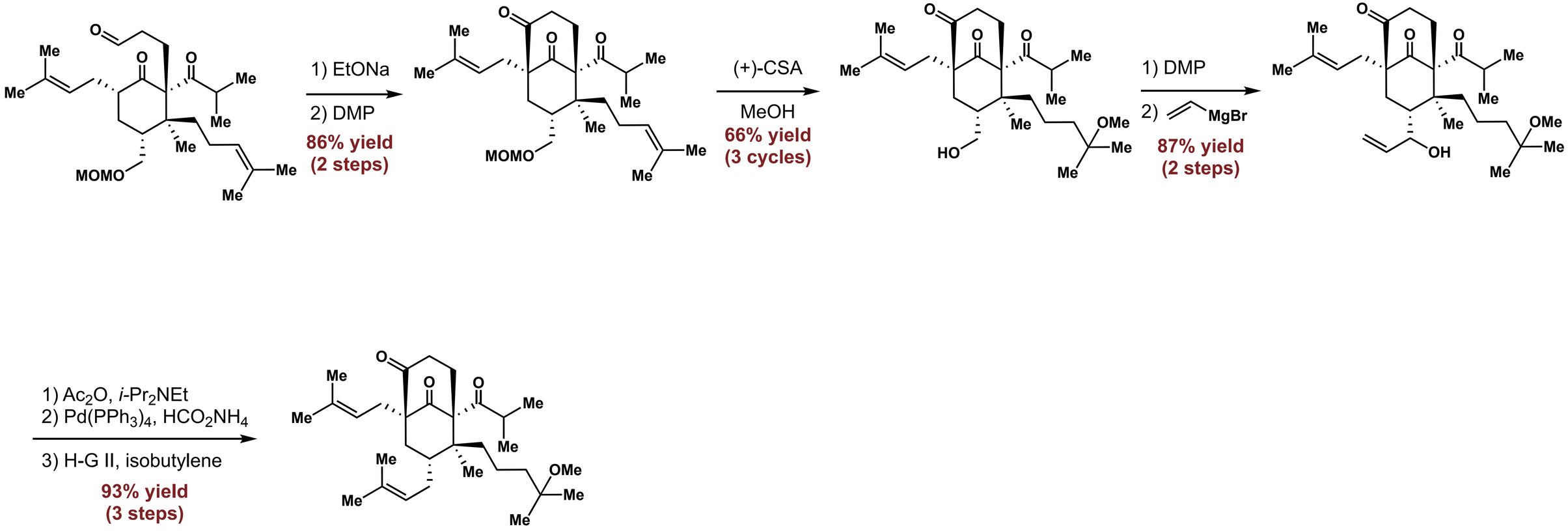

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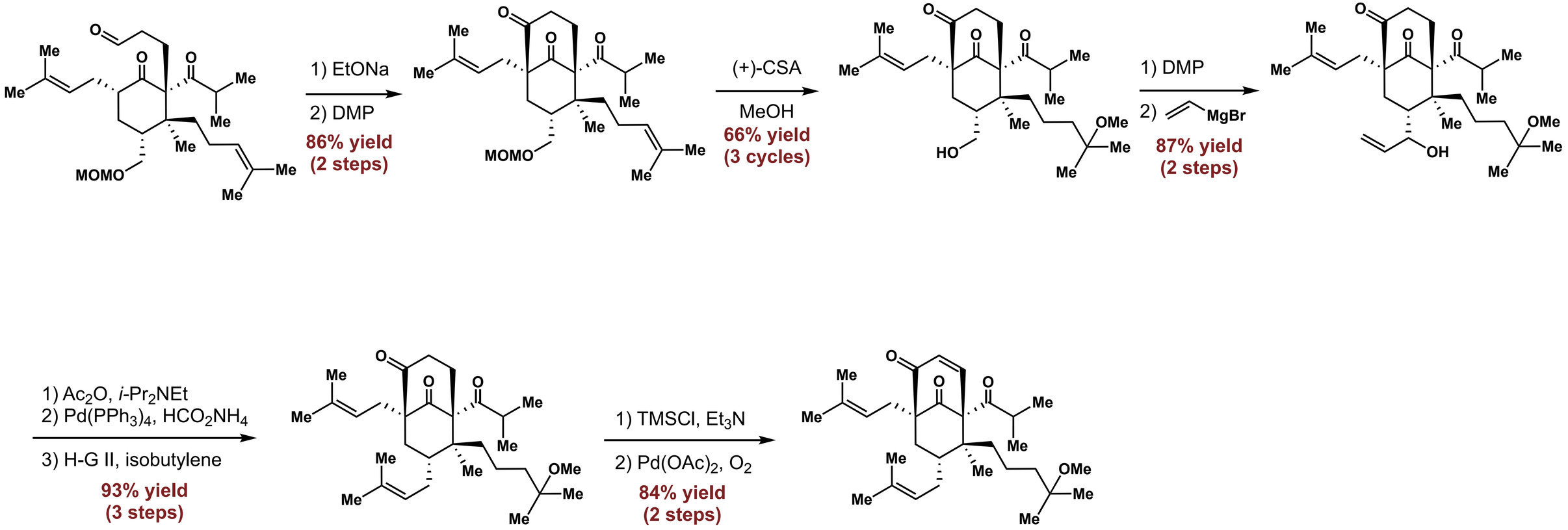

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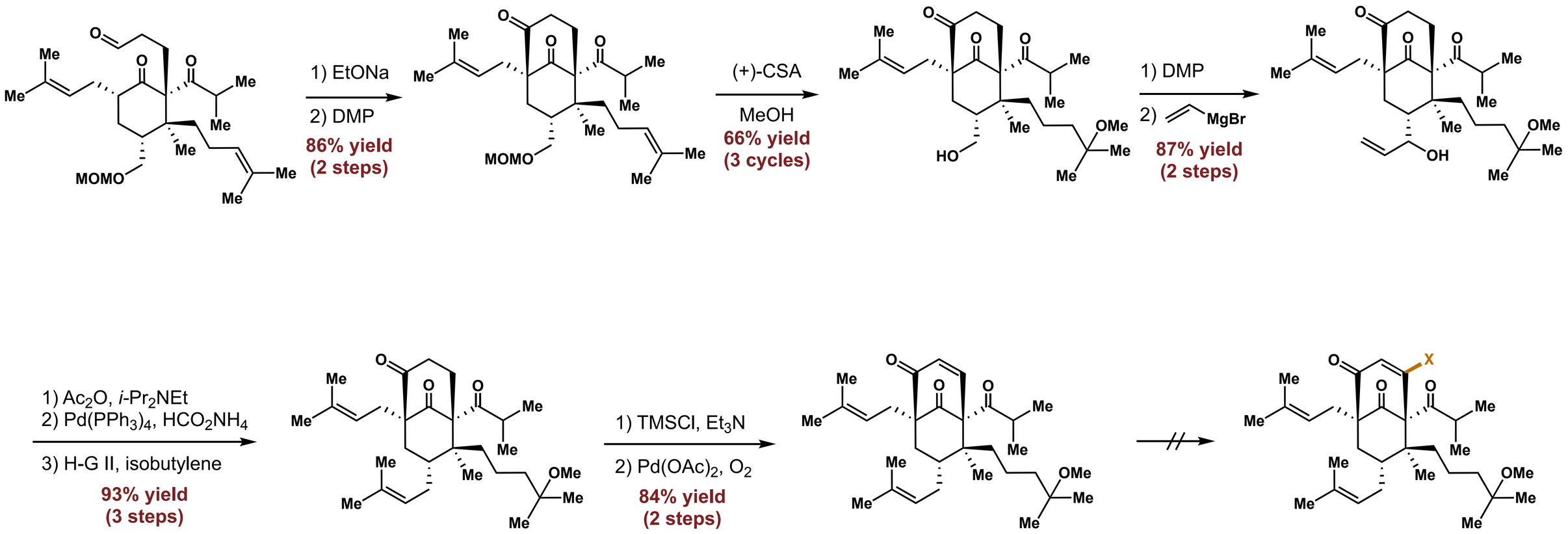

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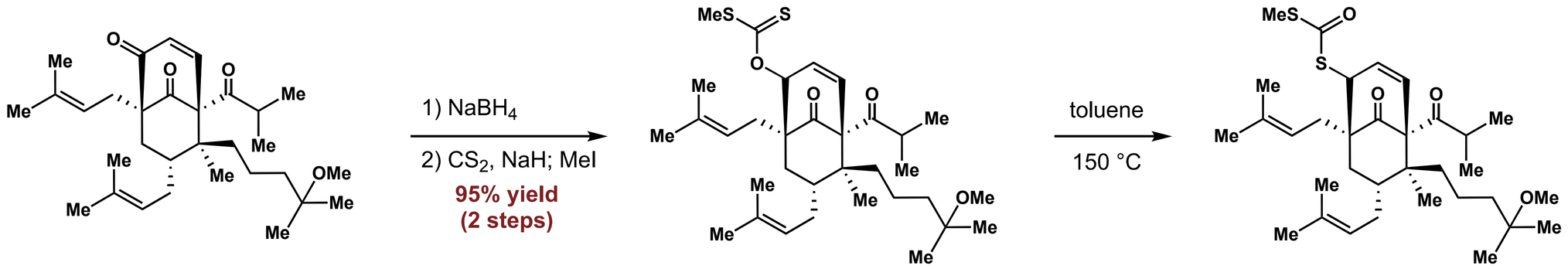

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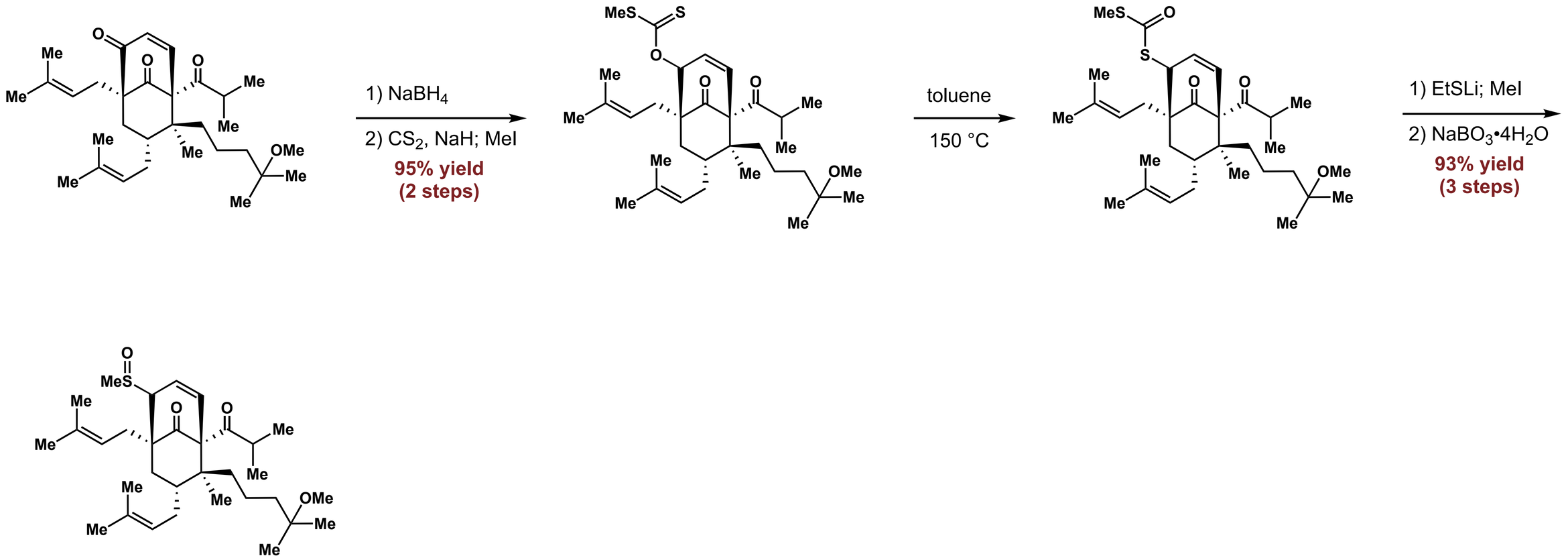

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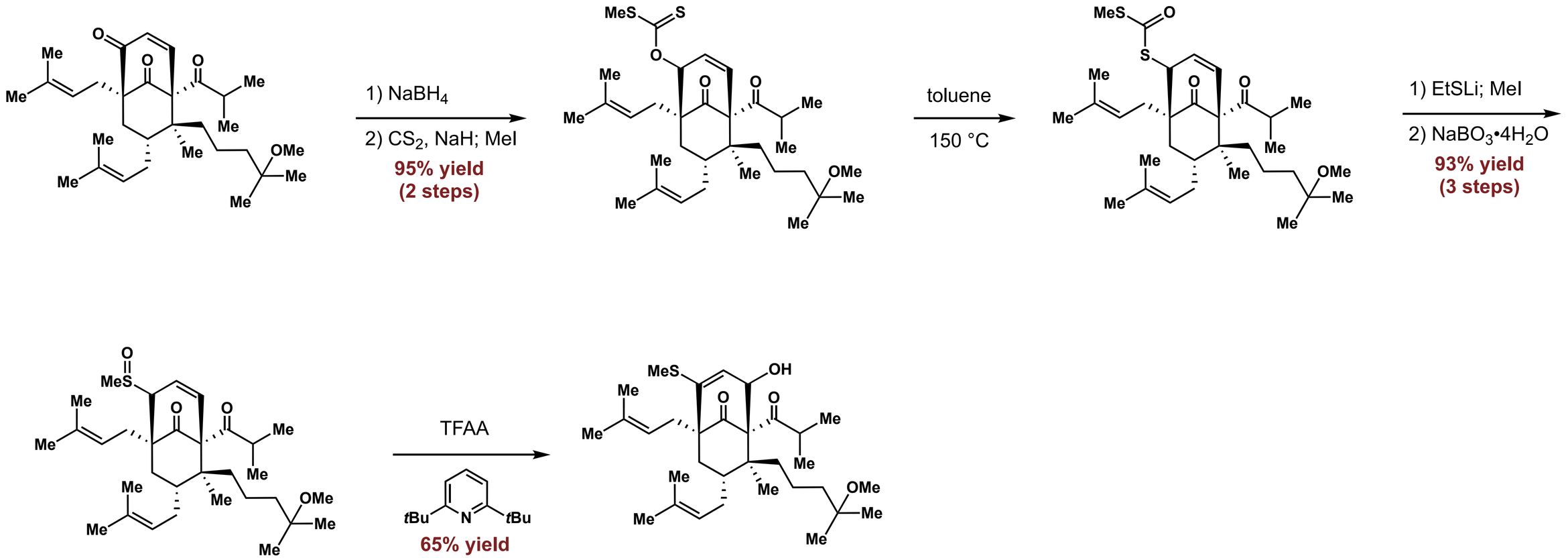

Pummerer Rearrangement

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Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103.

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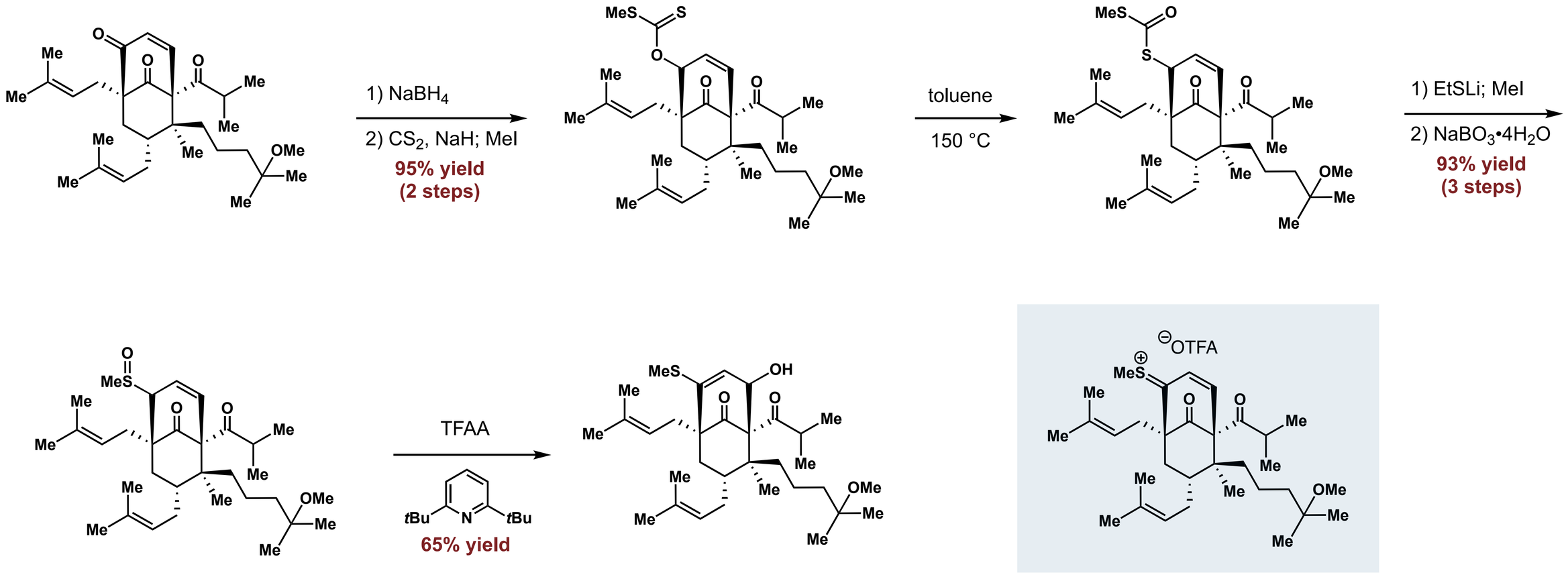

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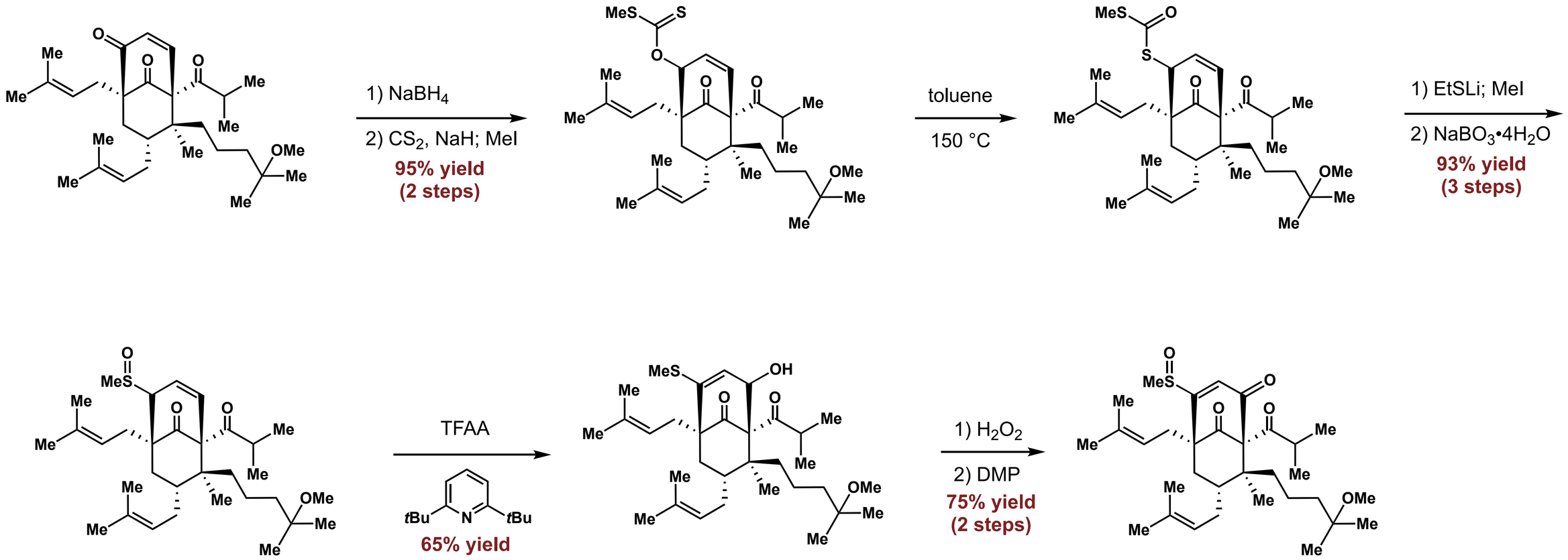

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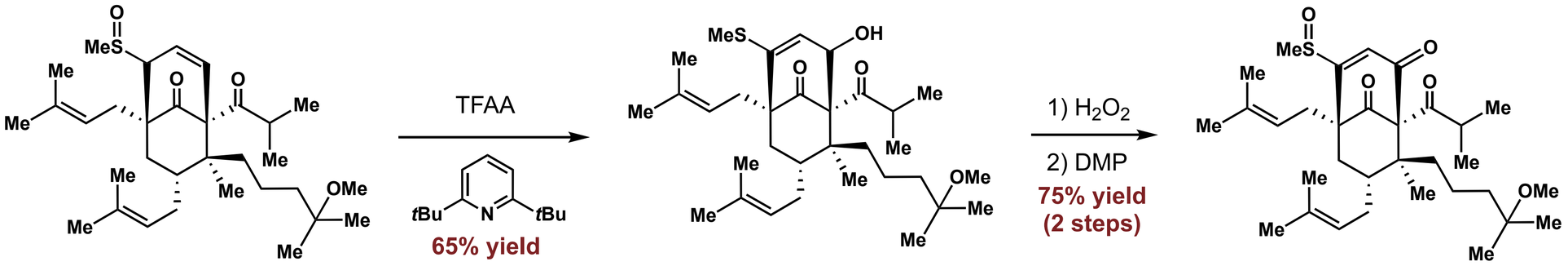

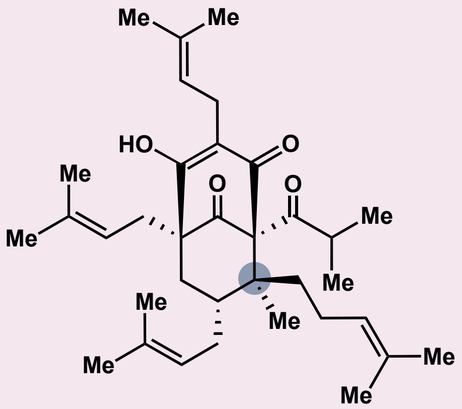

ent-Hyperforin

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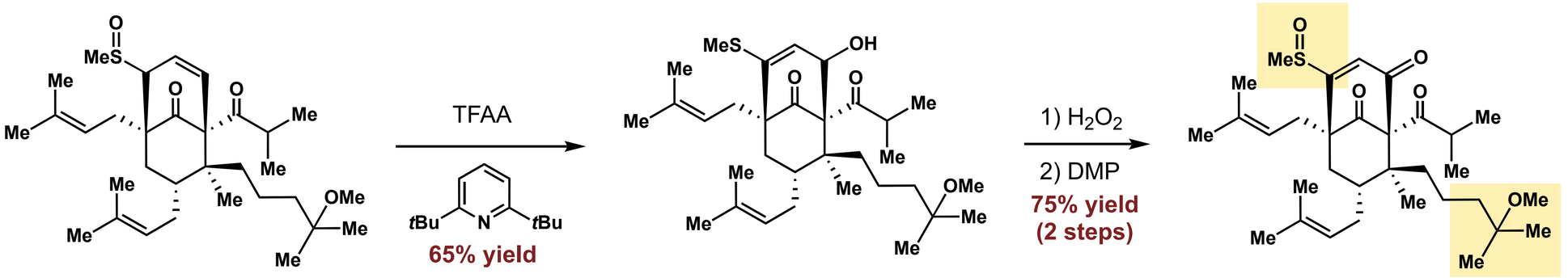

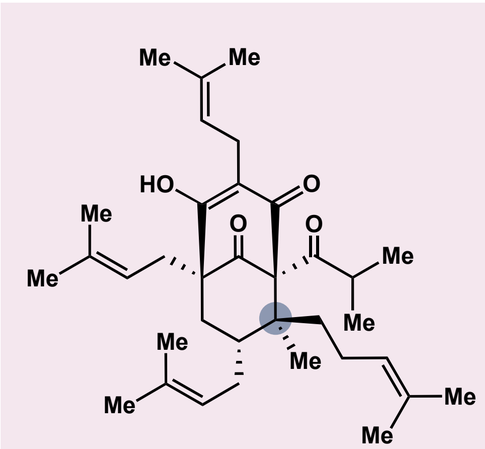

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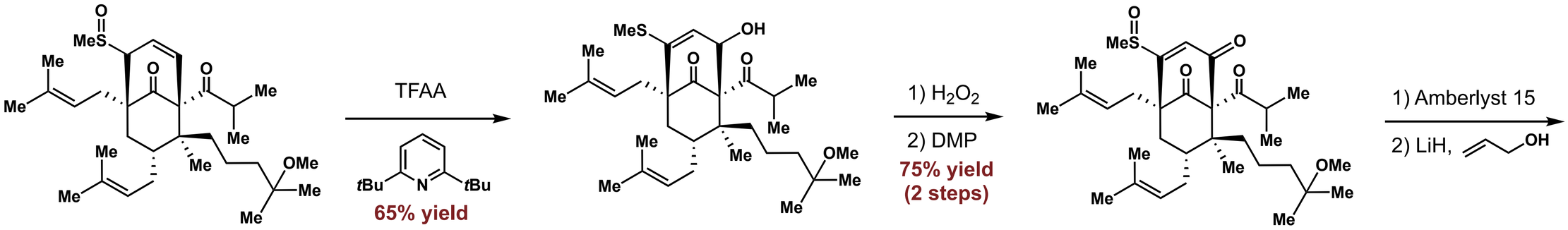

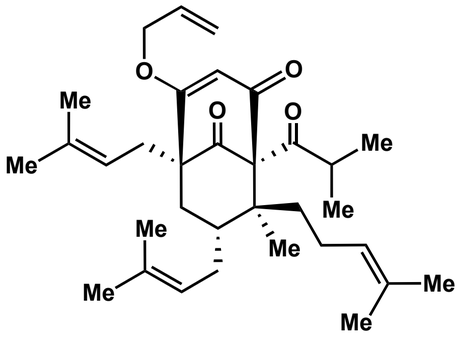

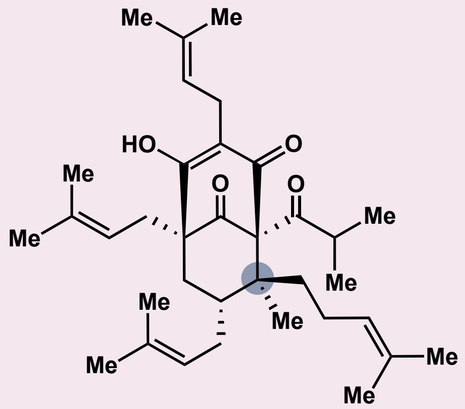

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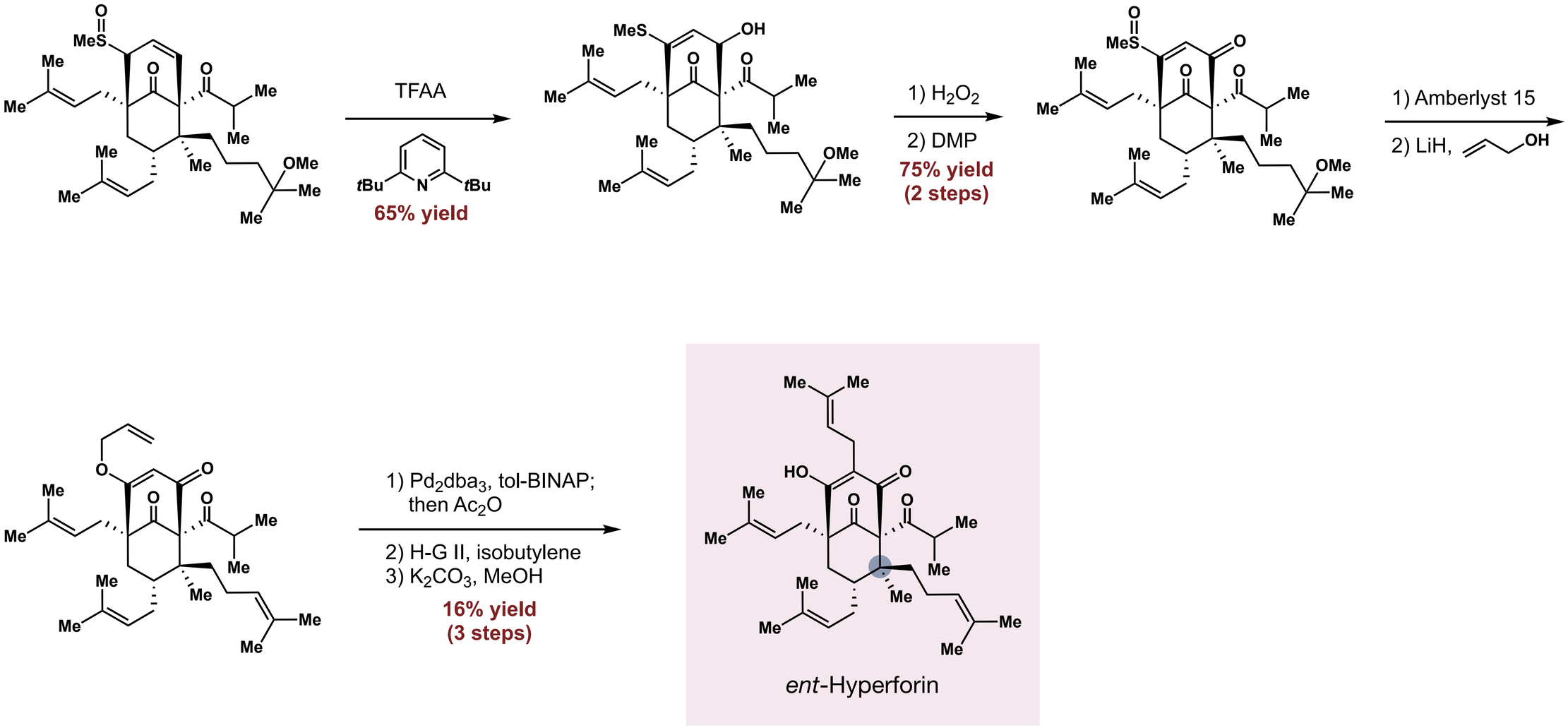

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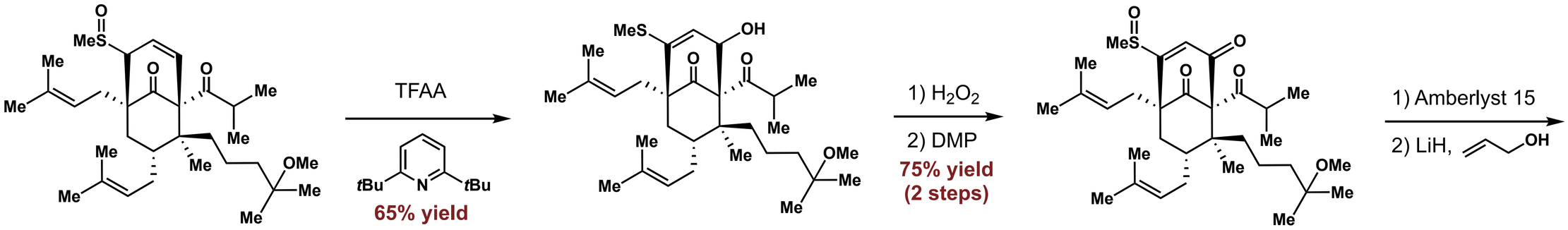

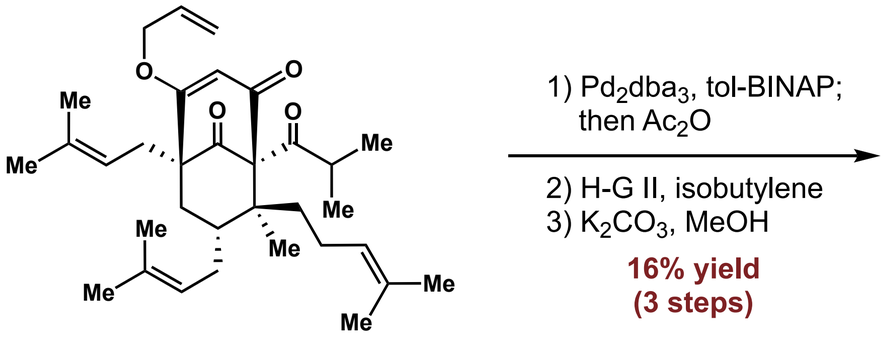

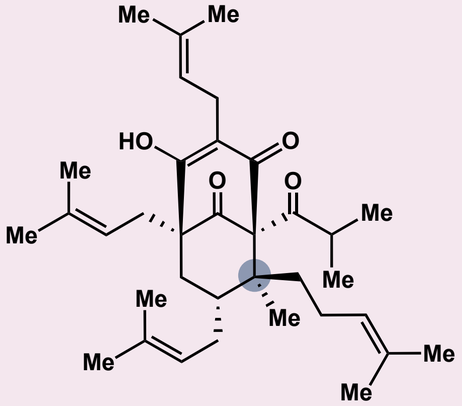

ent-Hyperforin

First total synthesis

Enantioselective

51 steps LLS

Redox/protecting groups manipulations

Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2010**, *66*, 6569.
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Total Synthesis of Hyperforin: A Quest of Synthetic Efficiency

1971: Isolation

2010: M. Shibasaki (**51 steps LLS**)

2013: M. Shair (**18 steps LLS**)

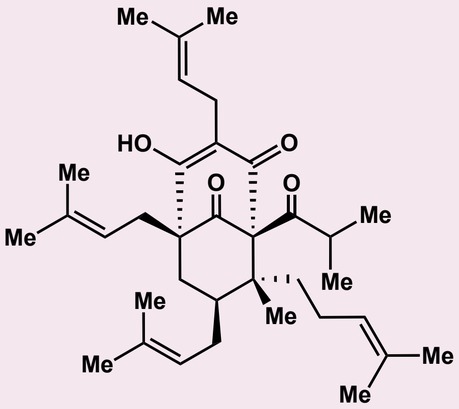
2015: T. Maimone (**10 steps LLS**)

2022: H. Li (**9 steps LLS**)

2014: L. Barriault (**17 steps LLS**)

1975: Structure Elucidation

2013: M. Nakada (**35 steps LLS**)

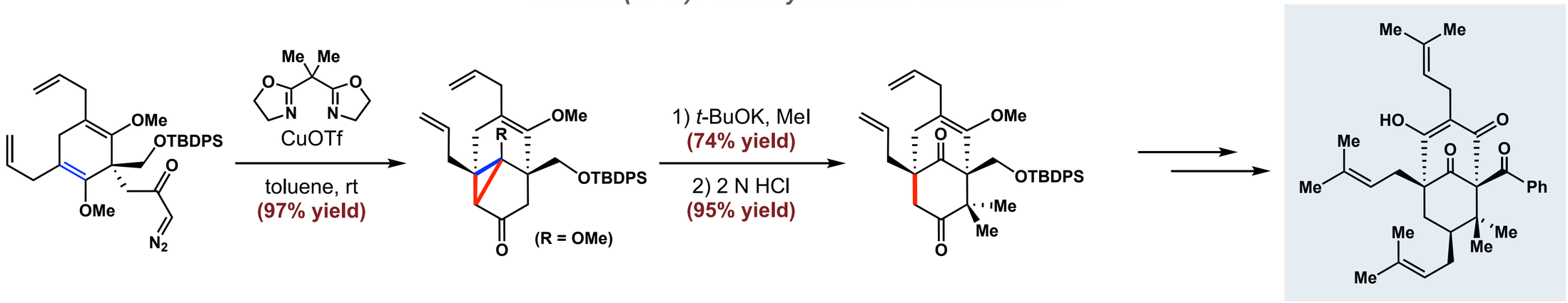


Hyperforin

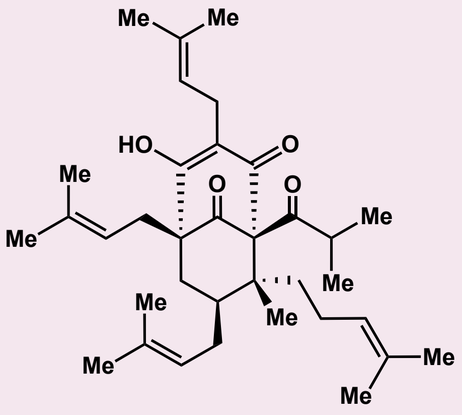
Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103.
Uwamori, M.; Nakada, M. *Tetrahedron Lett.* **2013**, *54*, 2022.
Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644.
Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701.
Ting, C. P.; Maimone, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 10516.
Li, Y.; Hong, B.; Franzoni, I.; Wang, M.; Guan, W.; Jia, H.; Li, H. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116136.

Total Synthesis of (±)-Hyperforin (Nakada)

Nakada (2010): Total Synthesis of Nemorosone



Abe, M.; Saito, A.; Nakada, M. *Tetrahedron Lett.* **2010**, *51*, 1298.



Hyperforin

Uwamori, M.; Saito, A.; Abe, M.; Nakada, M. *J. Org. Chem.* **2012**, *77*, 5098.
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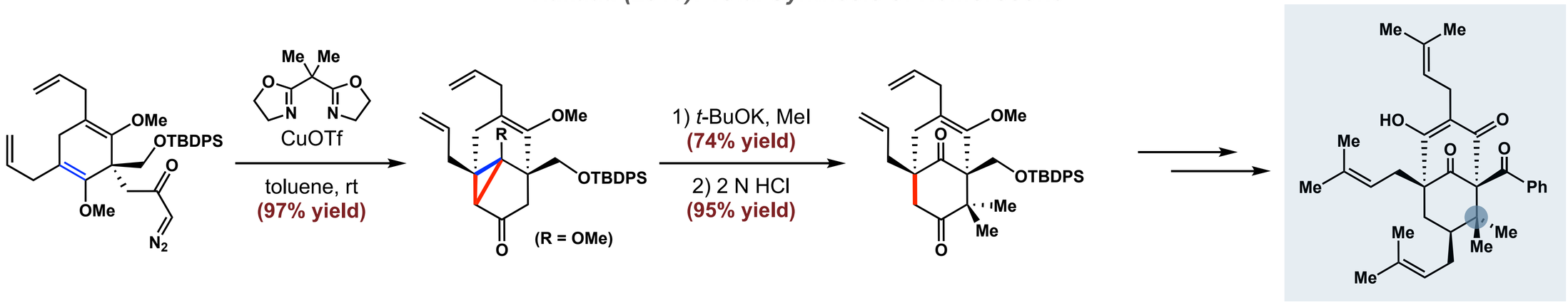

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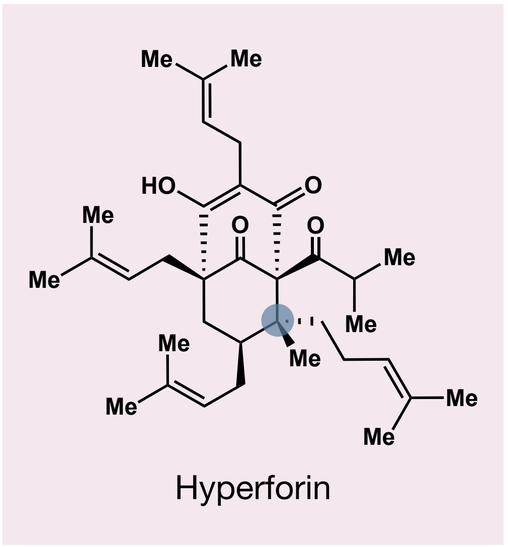

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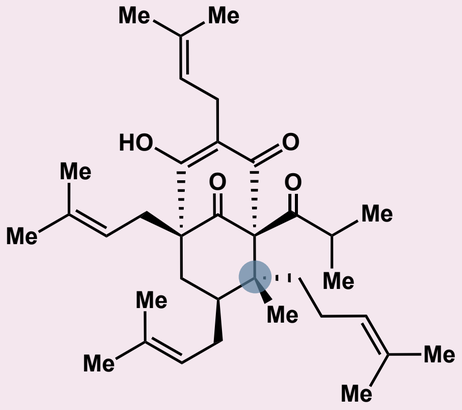

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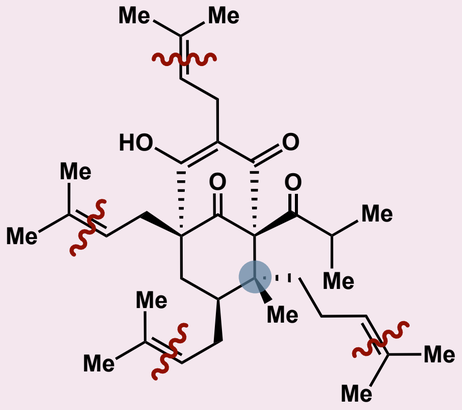

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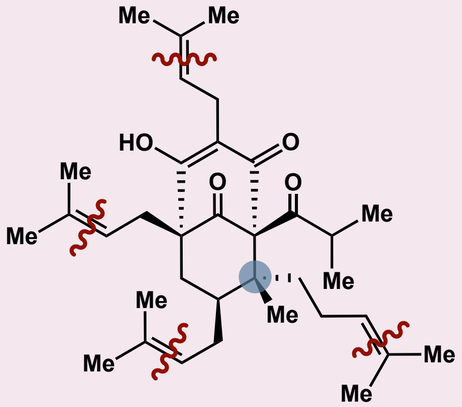
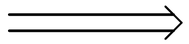
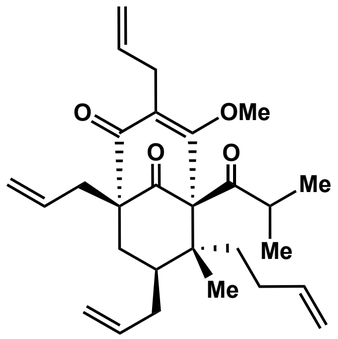


Hyperforin



Global Cross Metathesis



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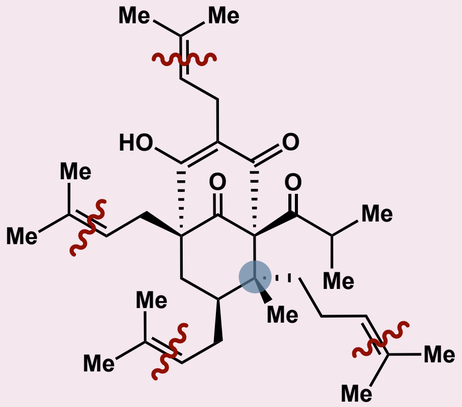
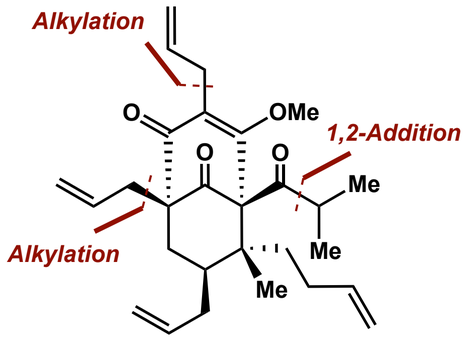
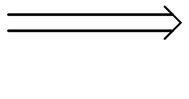
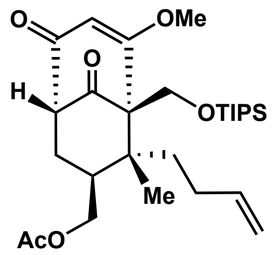


Hyperforin

Global Cross Metathesis







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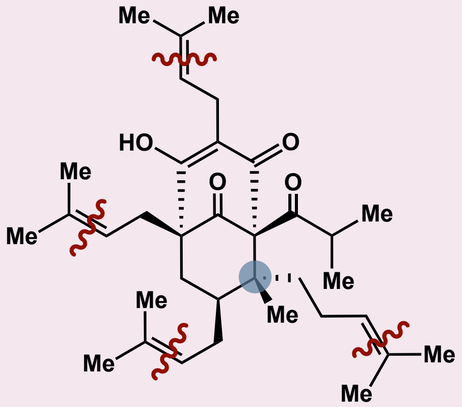
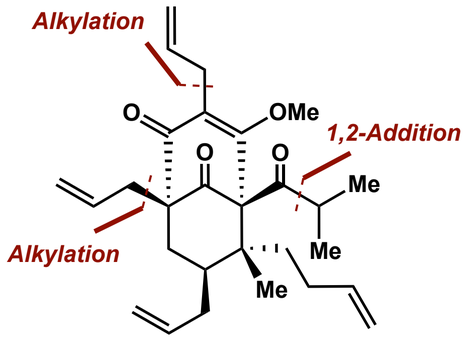
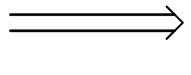
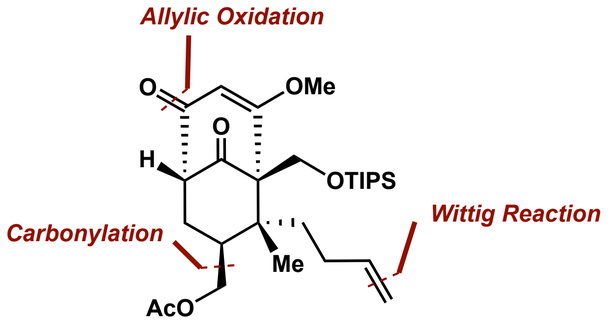


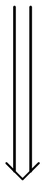
Hyperforin

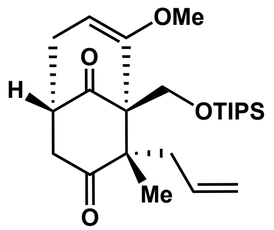
Global Cross Metathesis





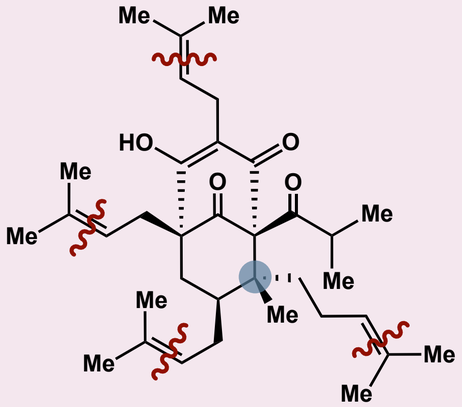






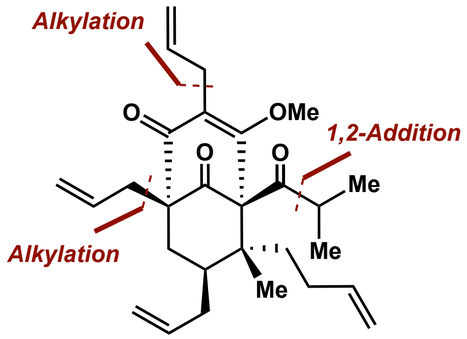
Uwamori, M.; Saito, A.; Abe, M.; Nakada, M. *J. Org. Chem.* **2012**, *77*, 5098.
Uwamori, M.; Nakada, M. *Tetrahedron Lett.* **2013**, *54*, 2022.

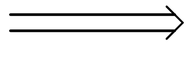
Total Synthesis of (±)-Hyperforin (Nakada)

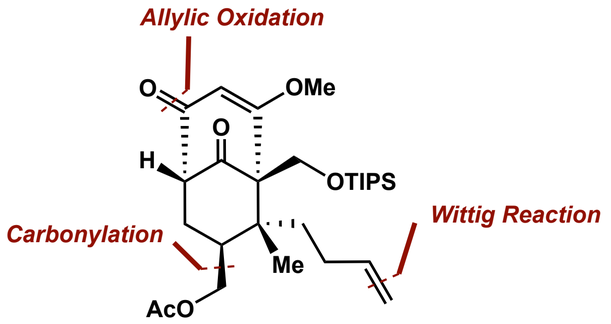


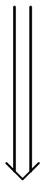
Hyperforin

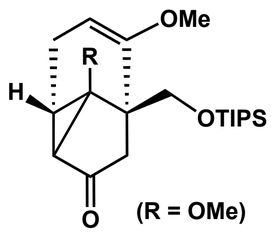
Global Cross Metathesis

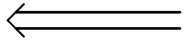


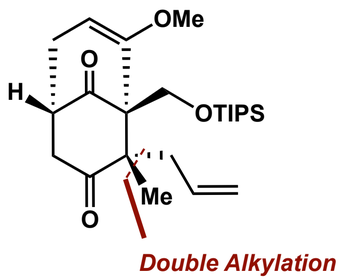












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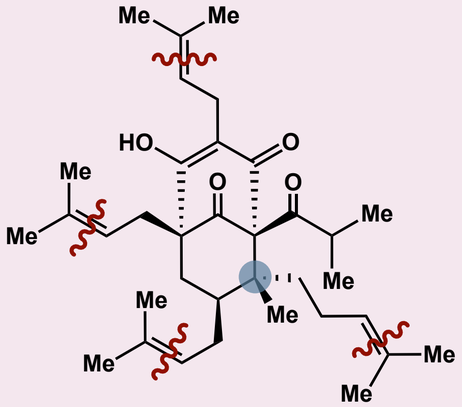
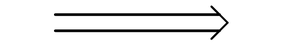
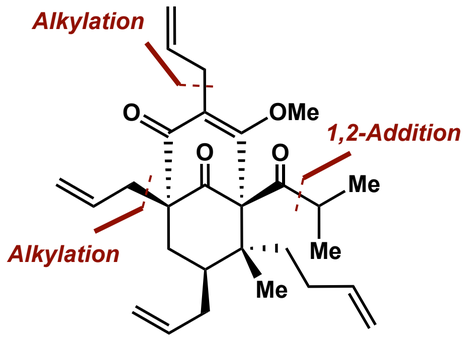
Total Synthesis of (±)-Hyperforin (Nakada)

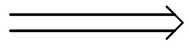


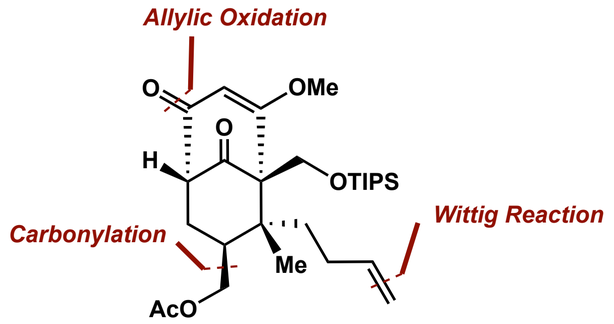
Hyperforin

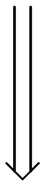


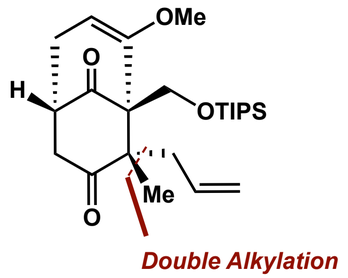
Global Cross Metathesis

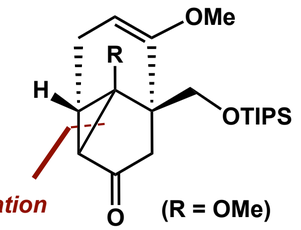


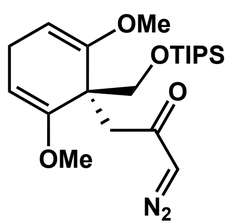


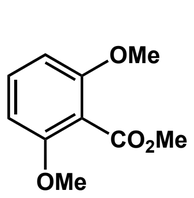












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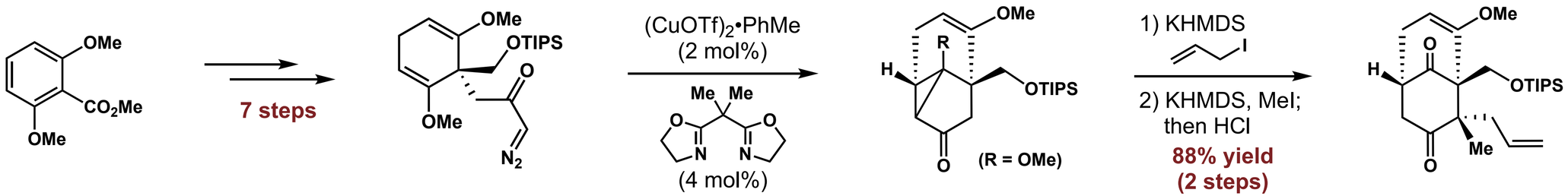
Uwamori, M.; Nakada, M. *Tetrahedron Lett.* **2013**, *54*, 2022.

Total Synthesis of (±)-Hyperforin (Nakada)



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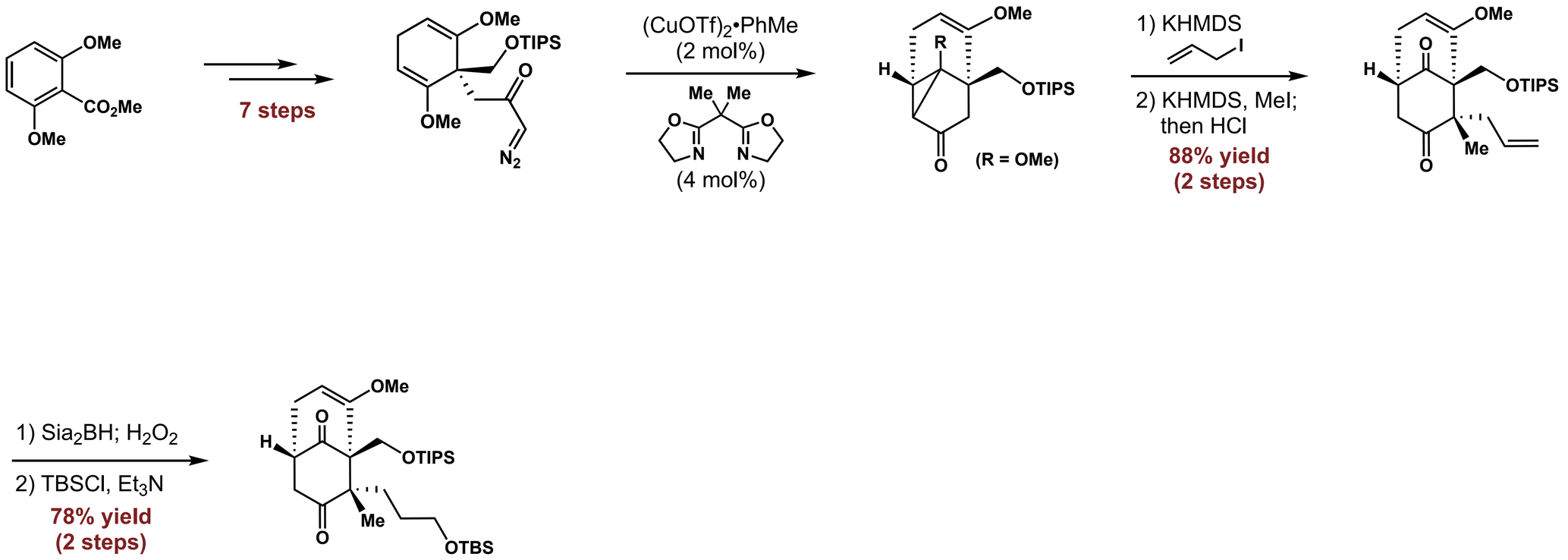

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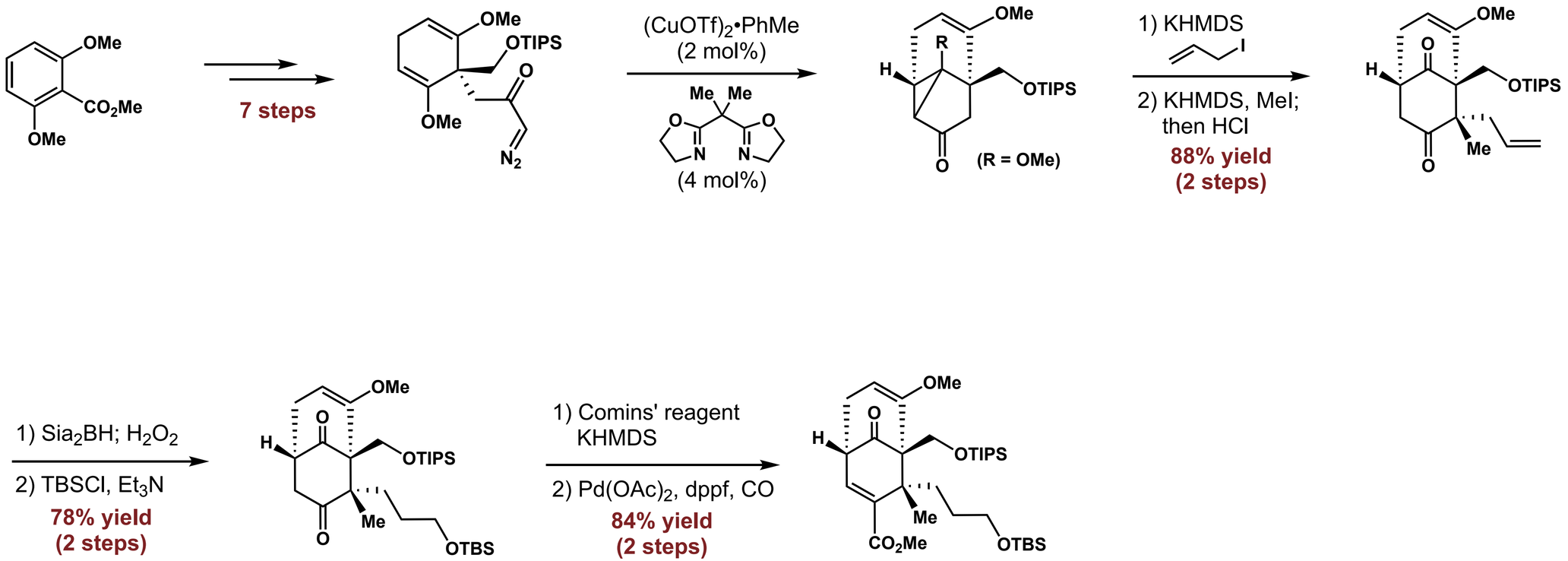

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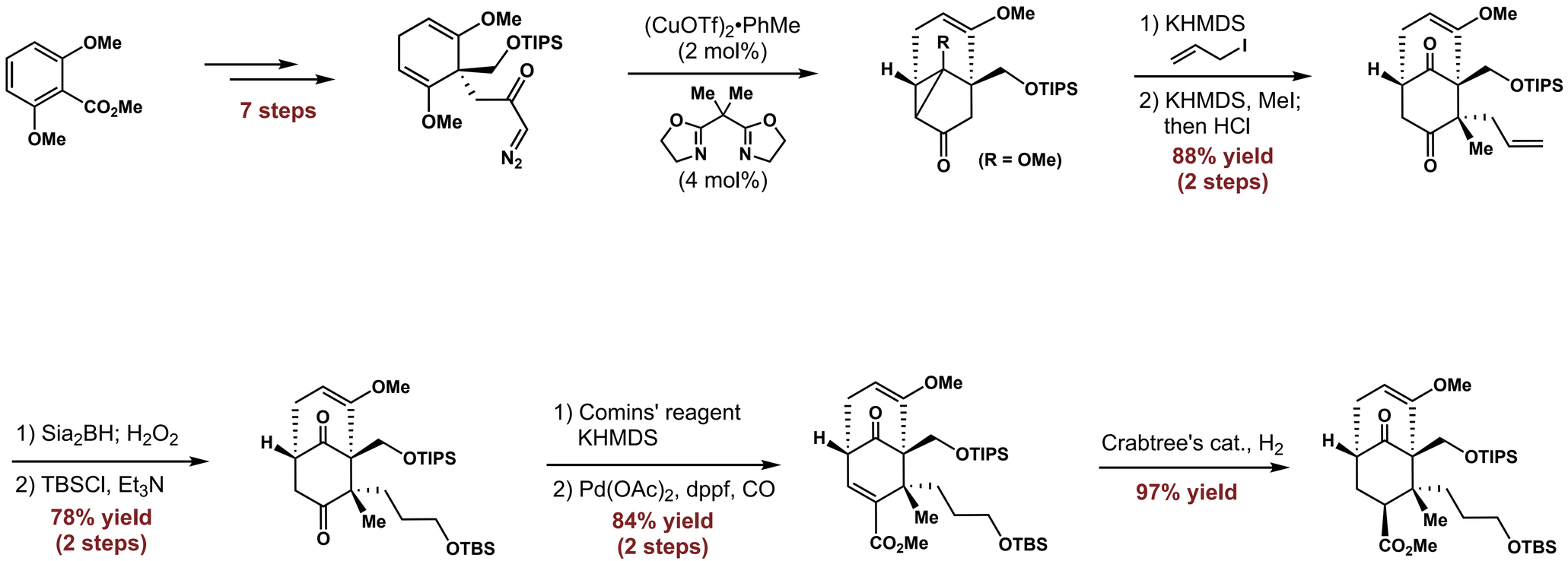

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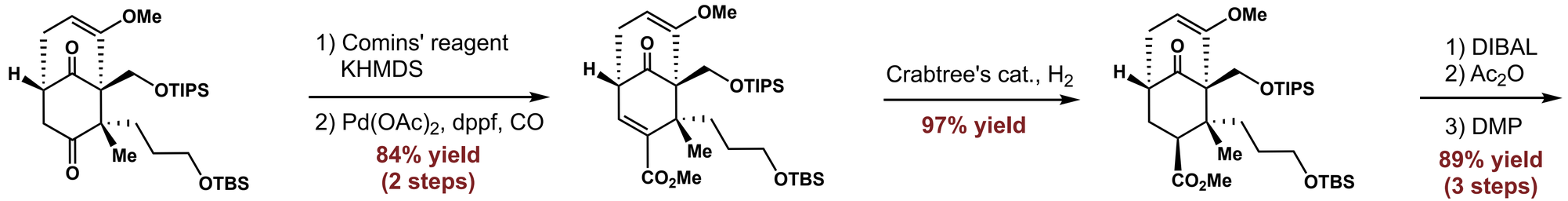

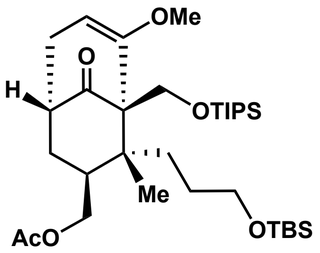

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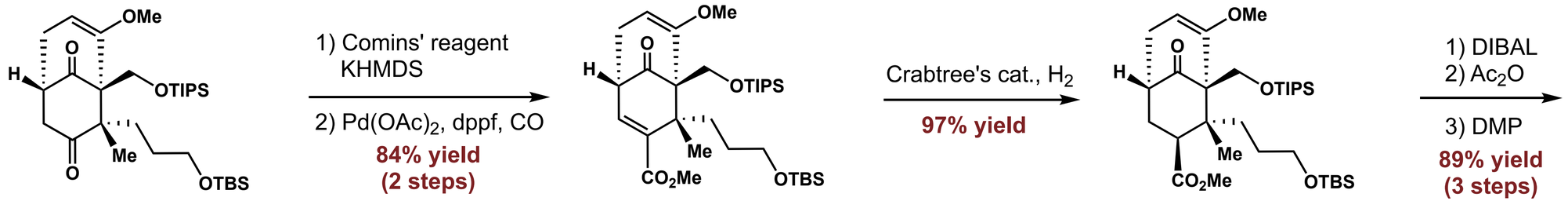

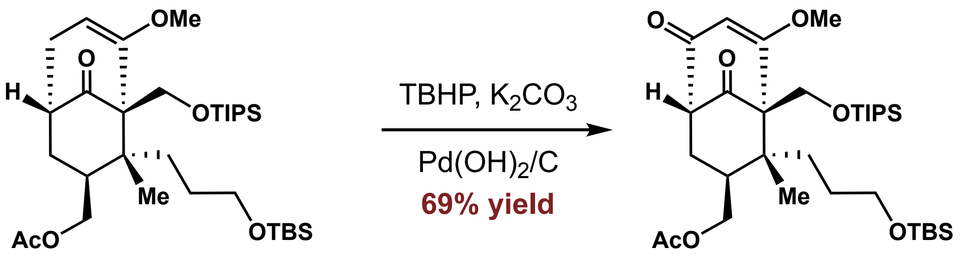

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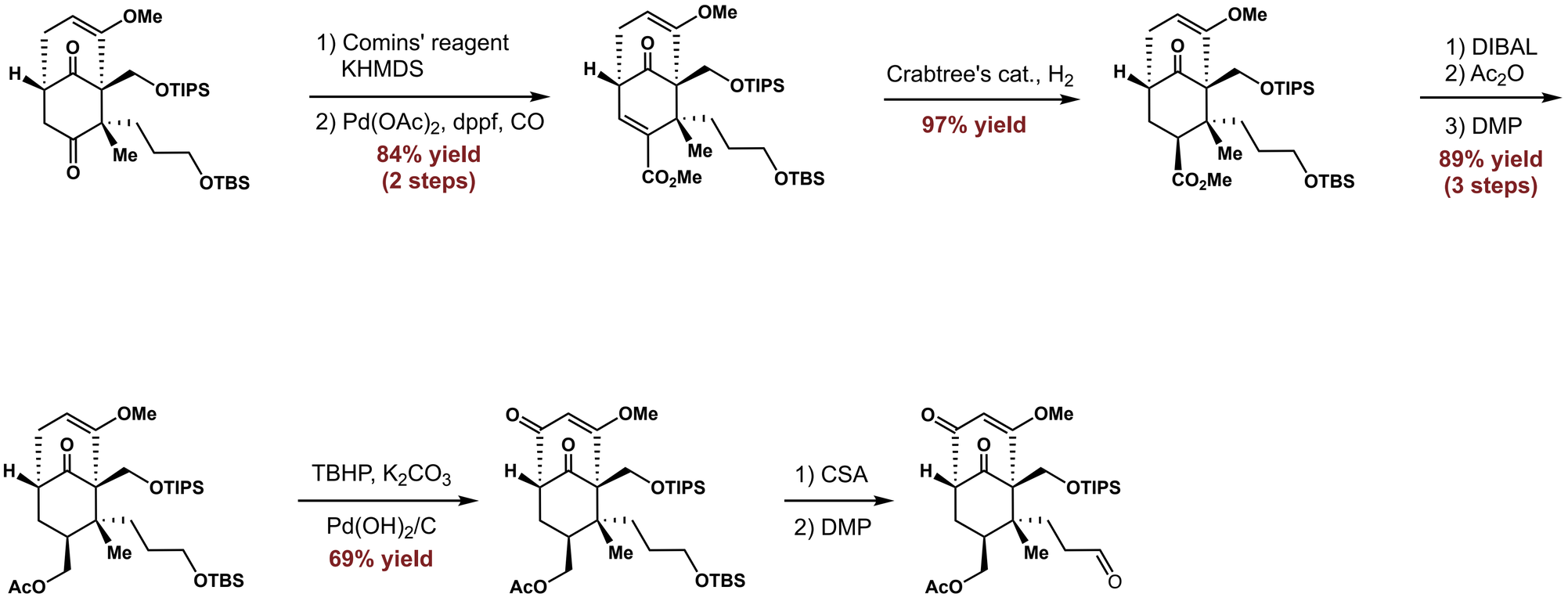

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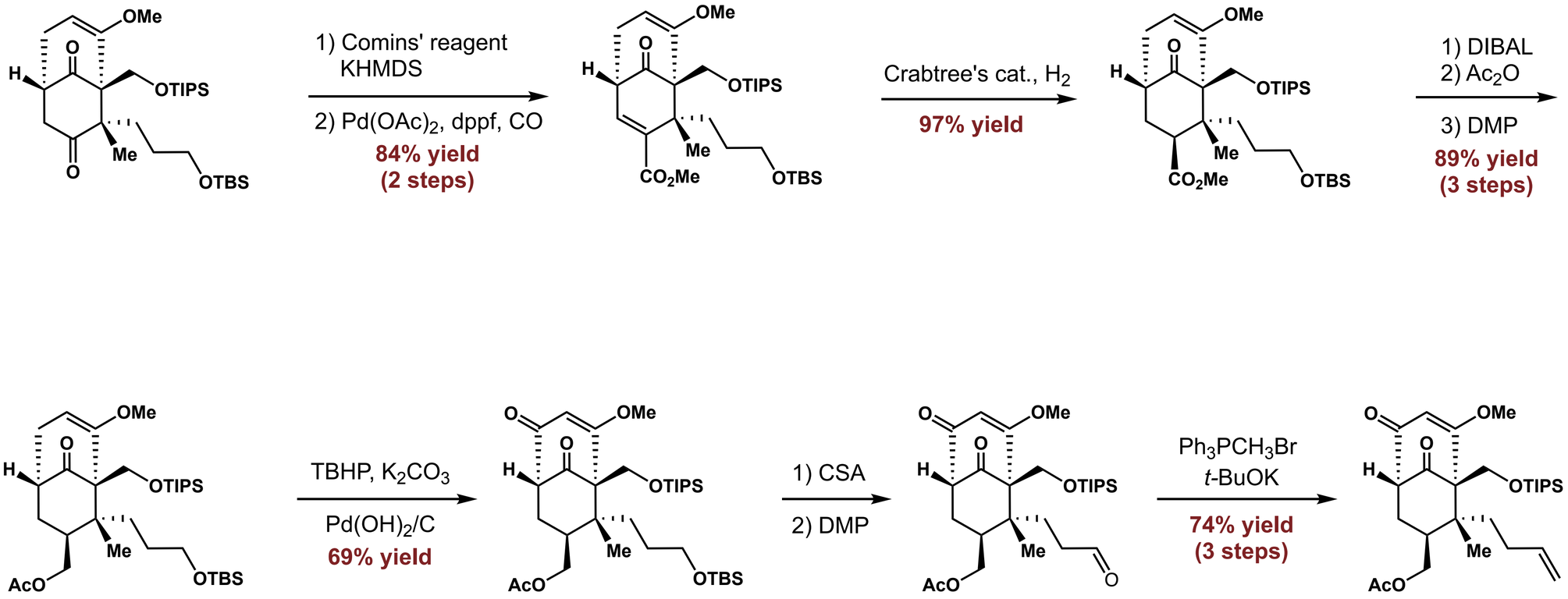

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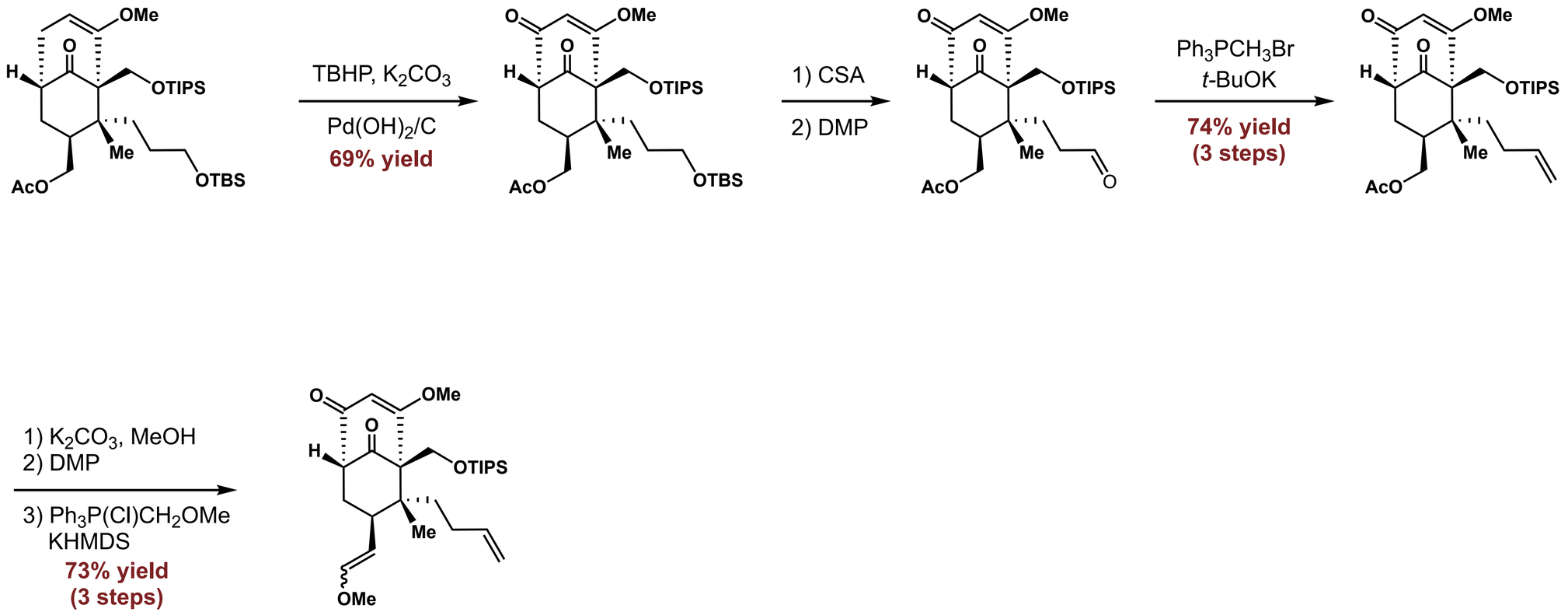

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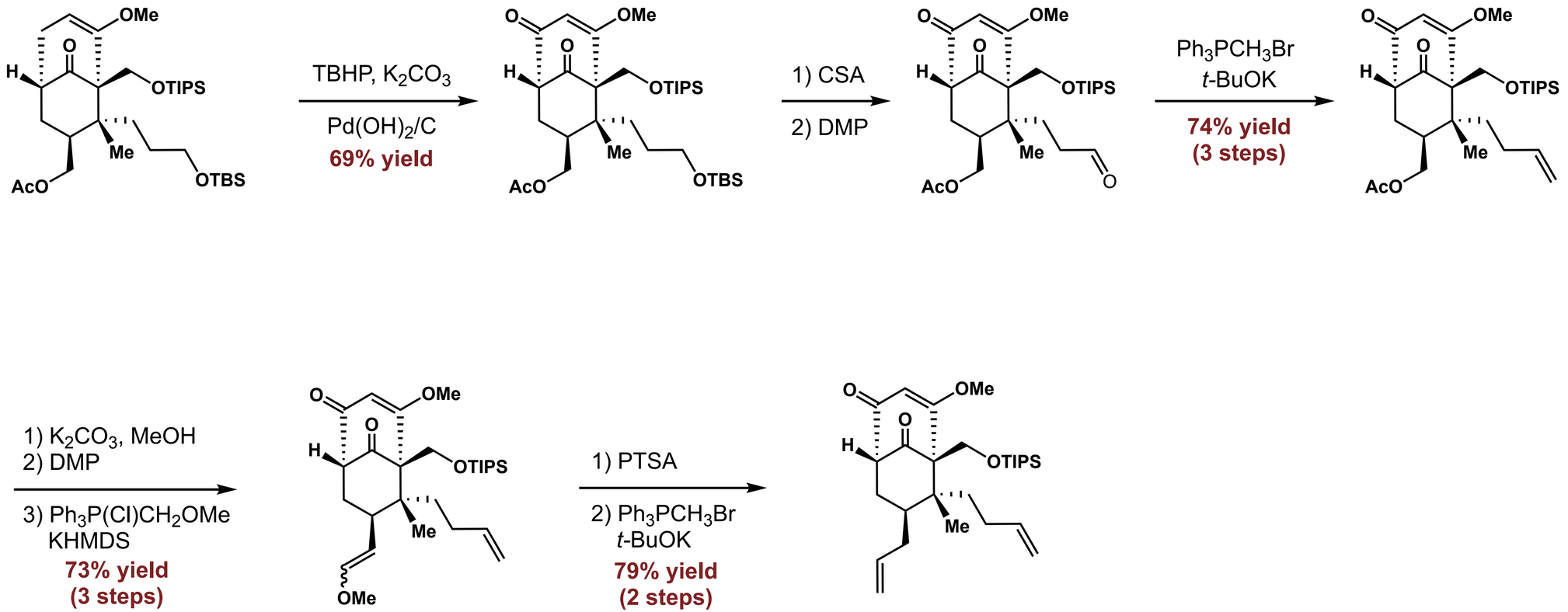

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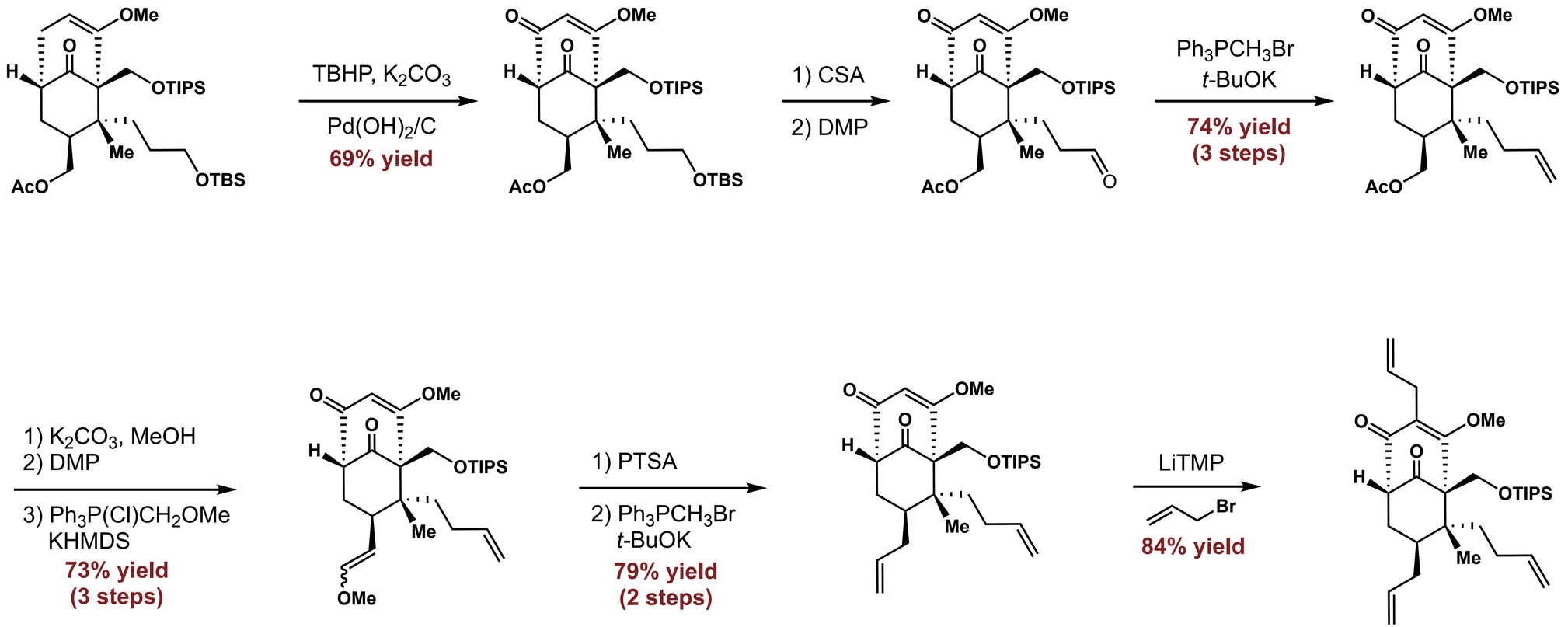

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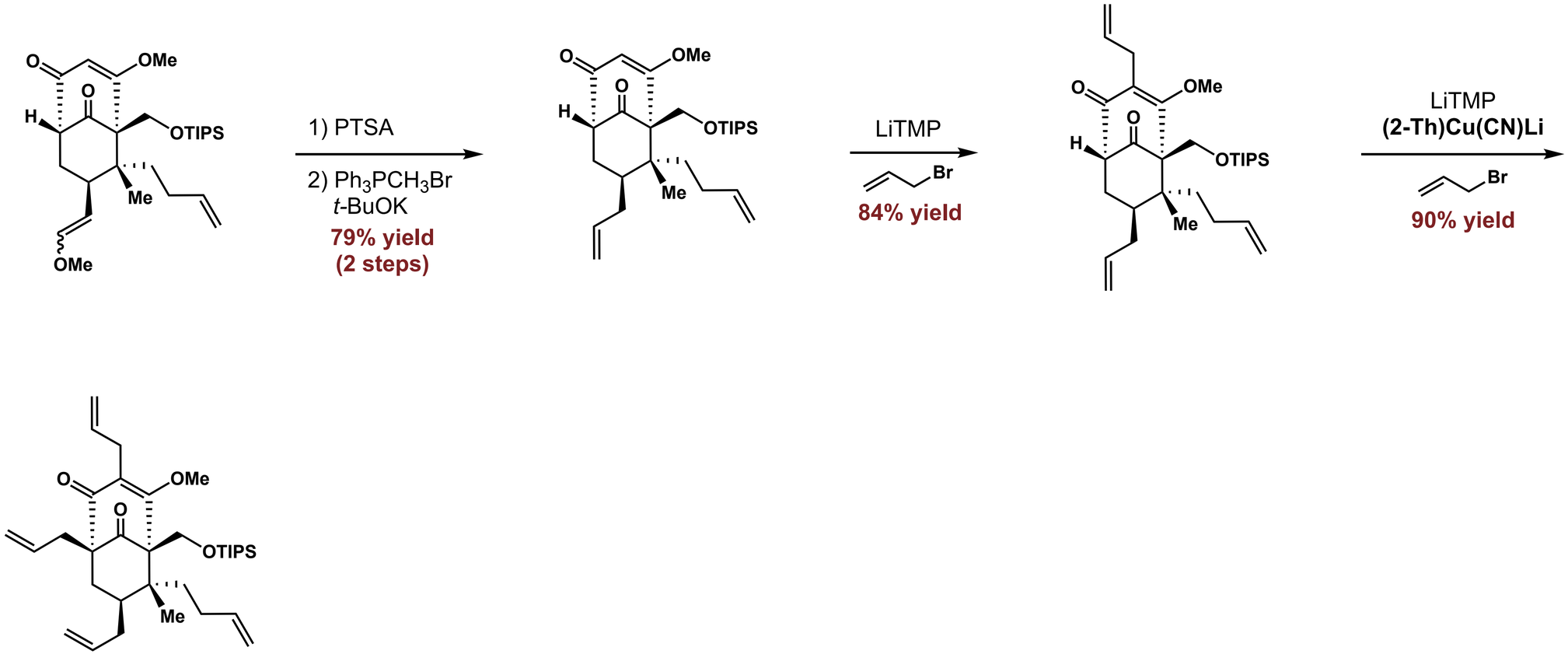

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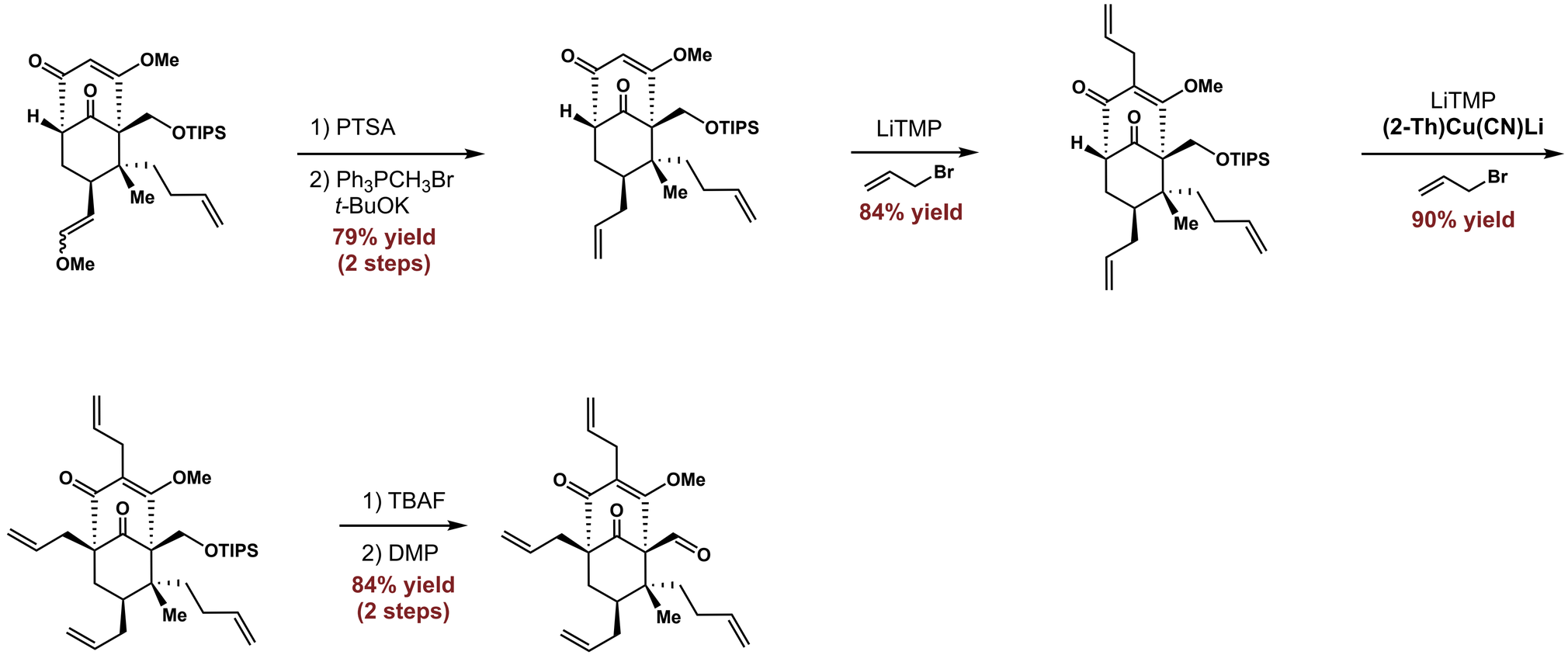

Uwamori, M.; Saito, A.; Abe, M.; Nakada, M. *J. Org. Chem.* **2012**, *77*, 5098.
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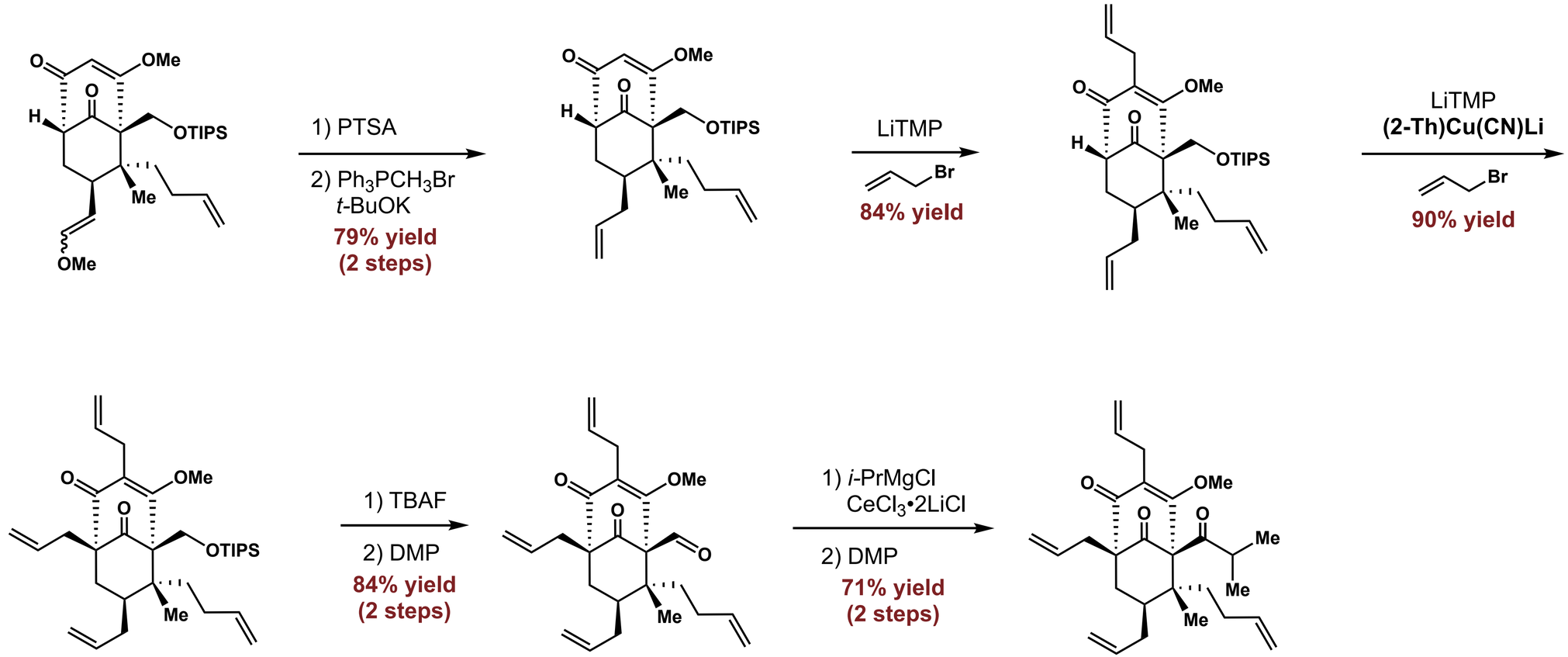

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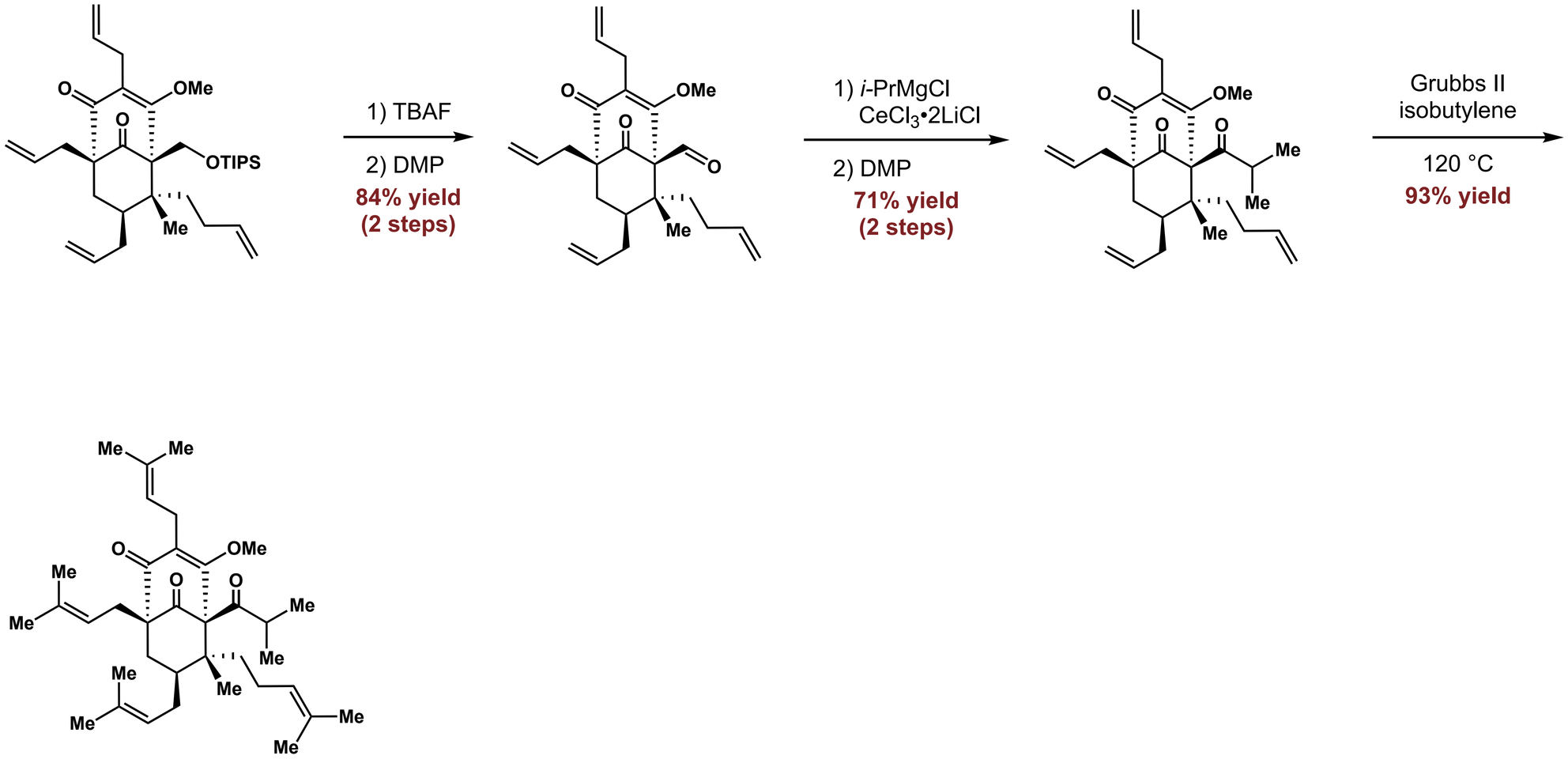

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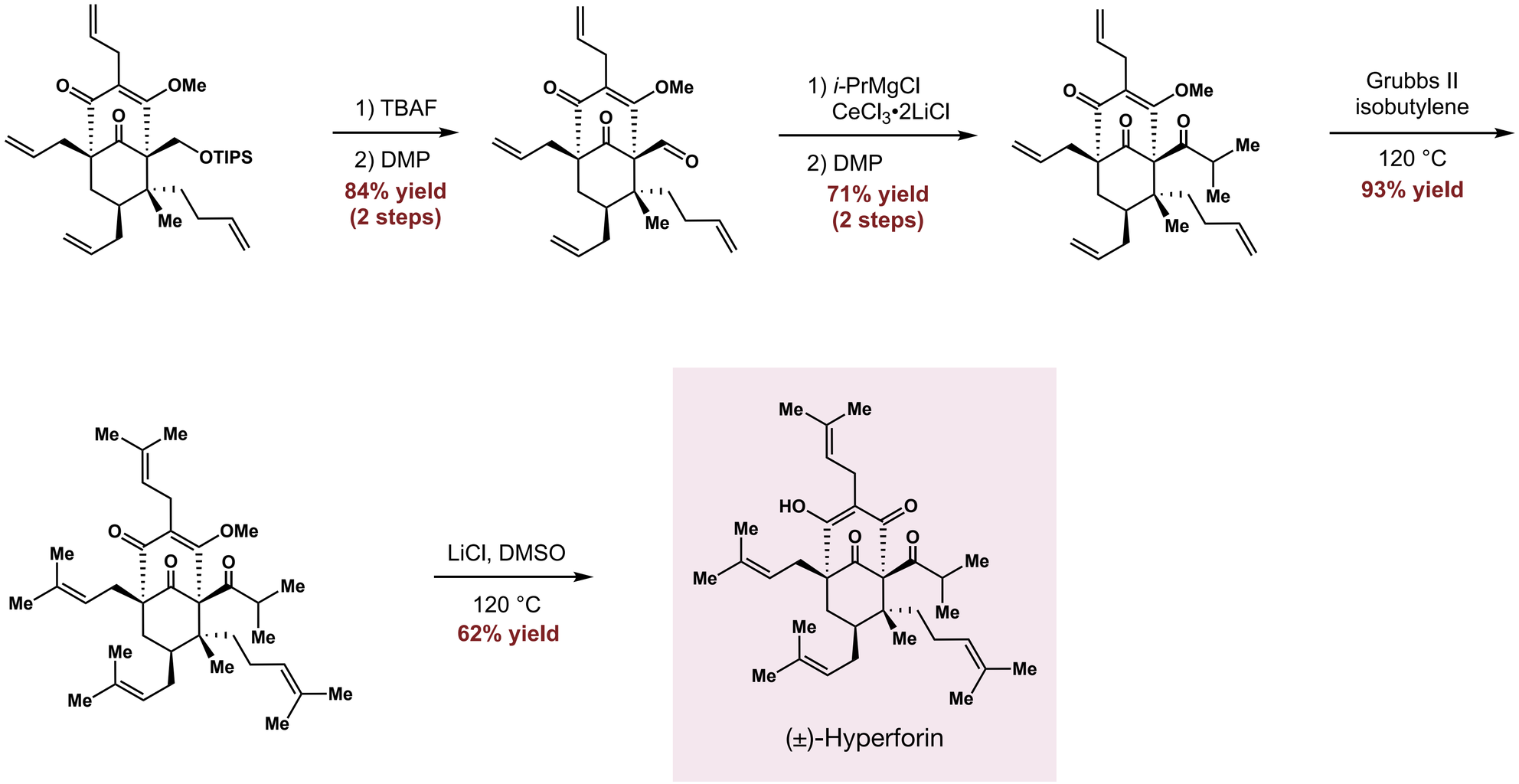

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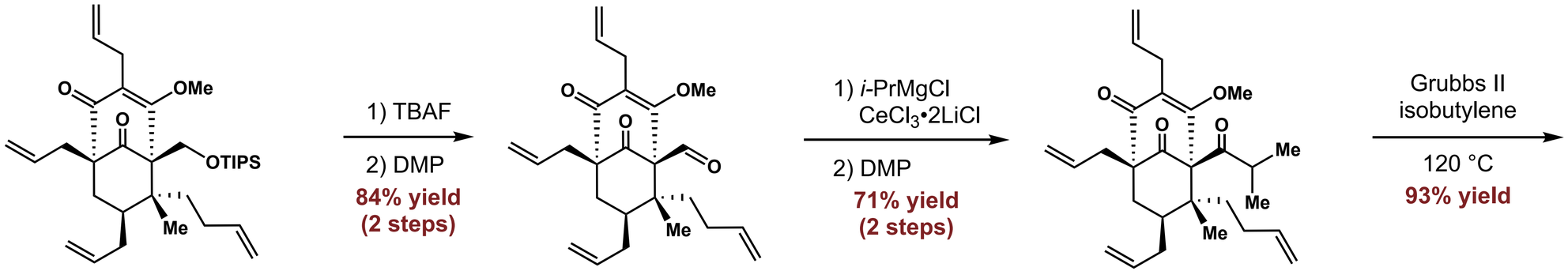
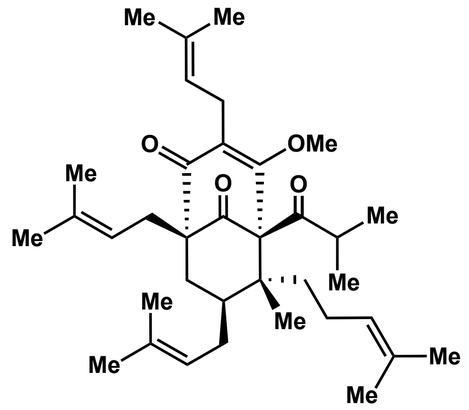
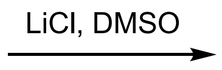
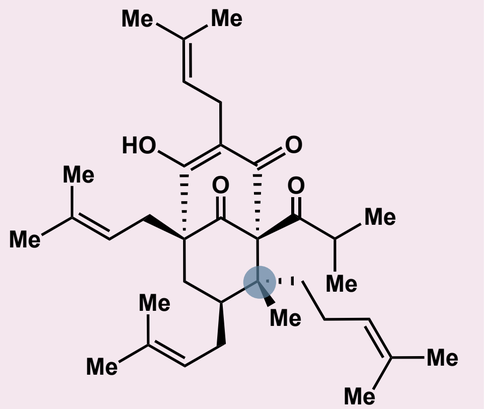








(±)-Hyperforin

Cyclopropanation

Global cross metathesis

35 steps LLS

Wittig homologation
Racemic synthesis

Uwamori, M.; Saito, A.; Abe, M.; Nakada, M. *J. Org. Chem.* **2012**, *77*, 5098.
Uwamori, M.; Nakada, M. *Tetrahedron Lett.* **2013**, *54*, 2022.

Total Synthesis of Hyperforin: A Quest of Synthetic Efficiency

1971: Isolation

2010: M. Shibasaki (**51 steps LLS**)

2013: M. Shair (**18 steps LLS**)

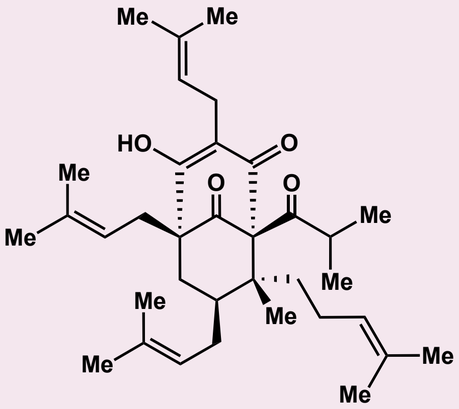
2015: T. Maimone (**10 steps LLS**)

2022: H. Li (**9 steps LLS**)

2014: L. Barriault (**17 steps LLS**)

1975: Structure Elucidation

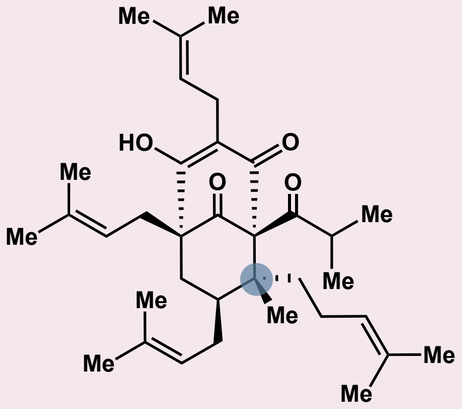
2013: M. Nakada (**35 steps LLS**)



Hyperforin

Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103.
Uwamori, M.; Nakada, M. *Tetrahedron Lett.* **2013**, *54*, 2022.
Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644.
Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701.
Ting, C. P.; Maimone, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 10516.
Li, Y.; Hong, B.; Franzoni, I.; Wang, M.; Guan, W.; Jia, H.; Li, H. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116136.

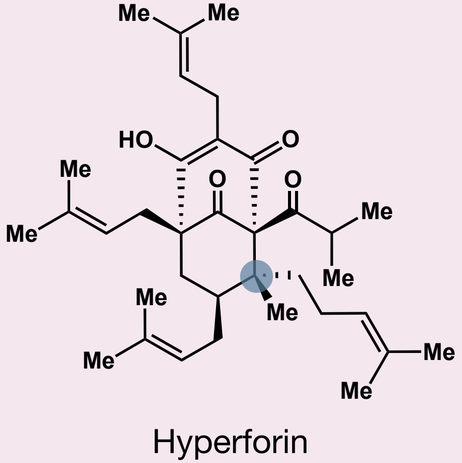
Total Synthesis of Hyperforin (Shair)



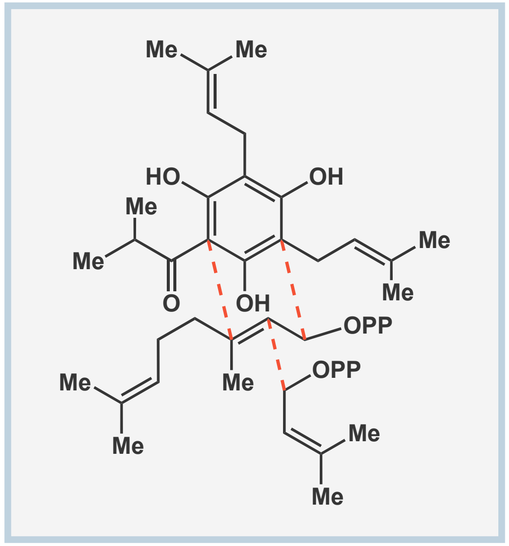
Hyperforin

Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644.

Total Synthesis of Hyperforin (Shair)



Hyperforin



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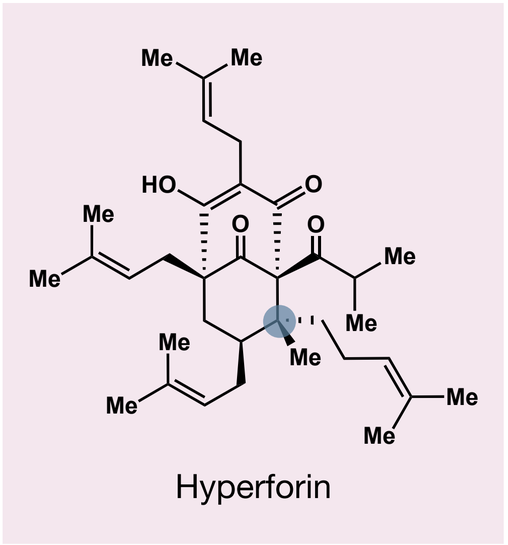

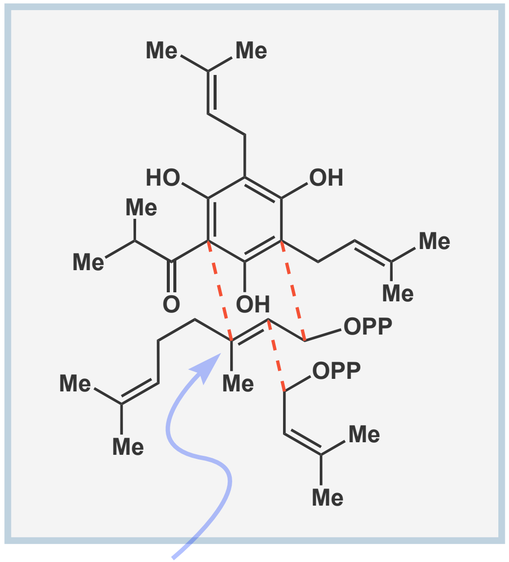

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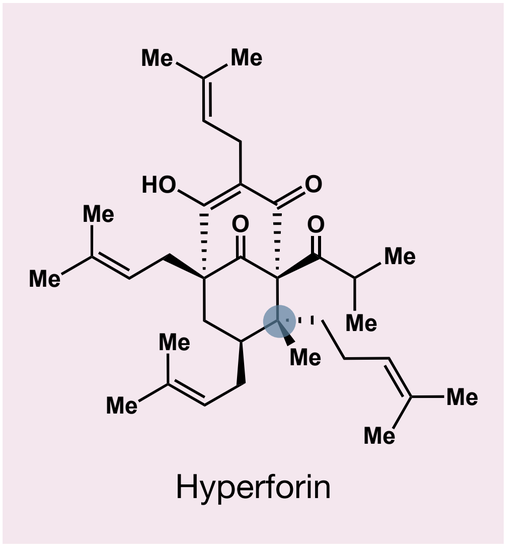

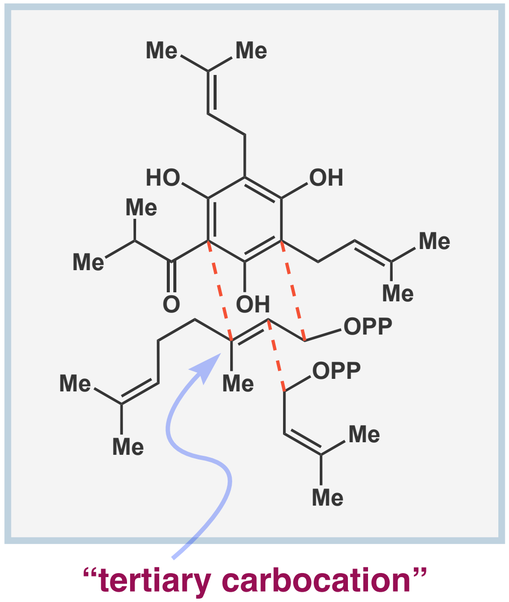

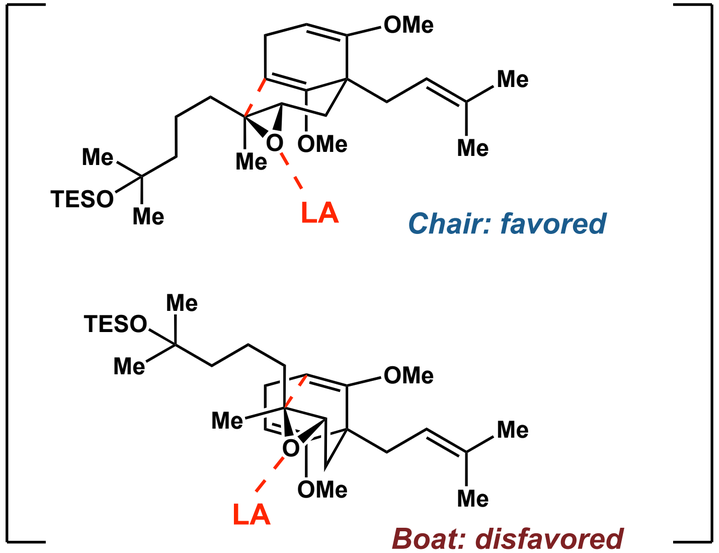

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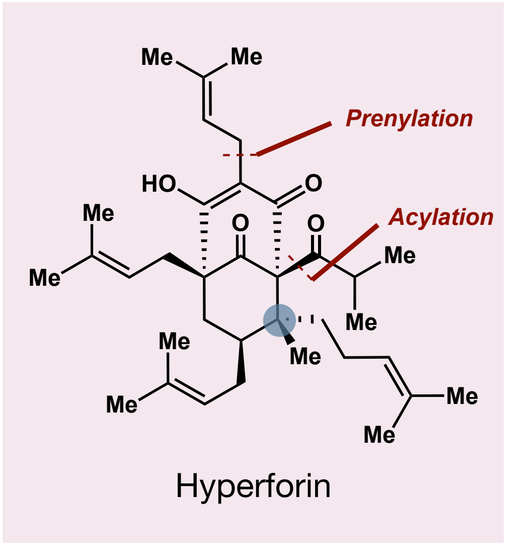

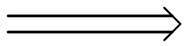

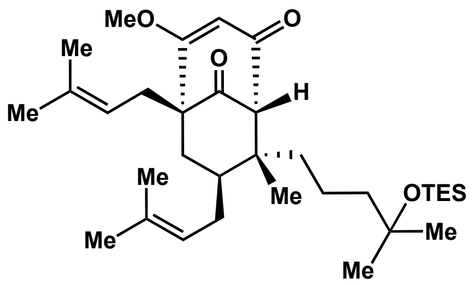

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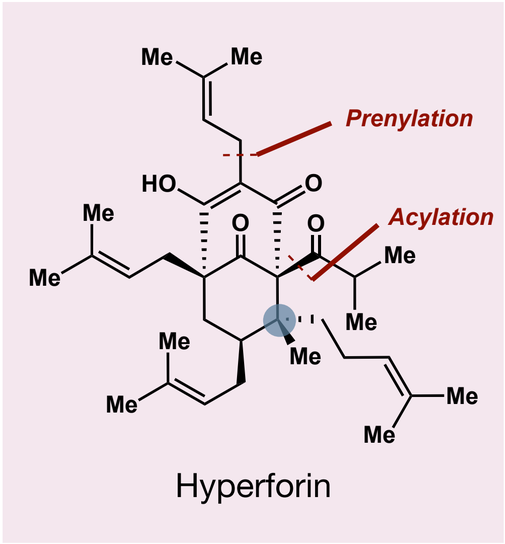

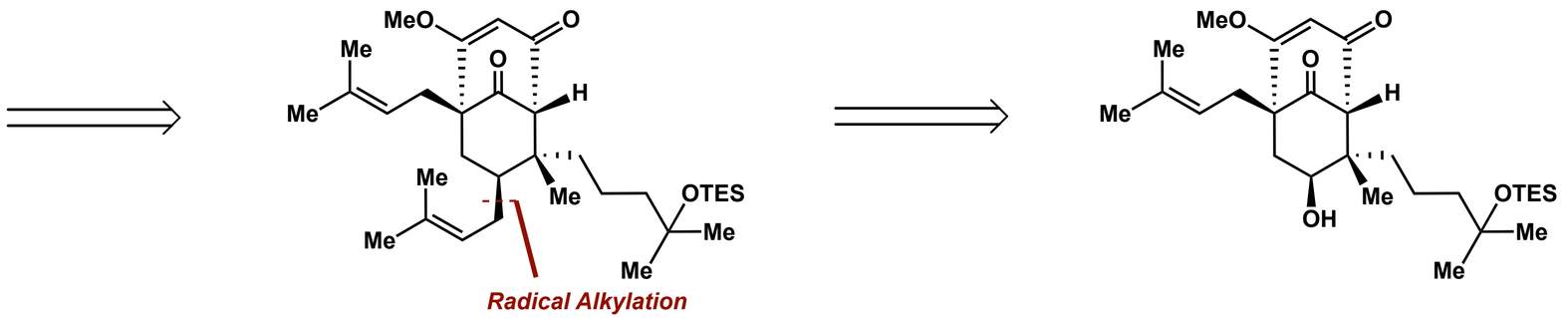

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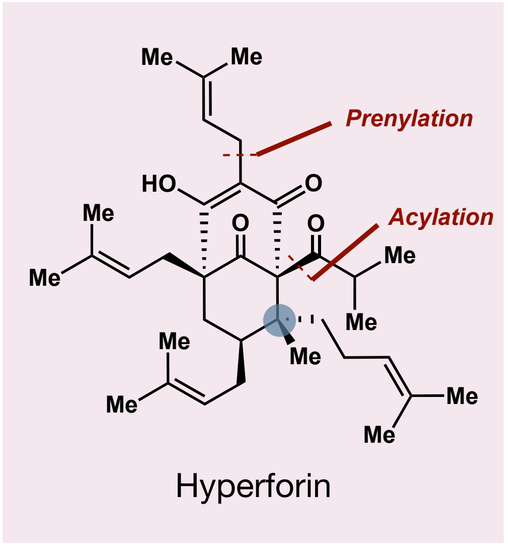

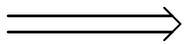

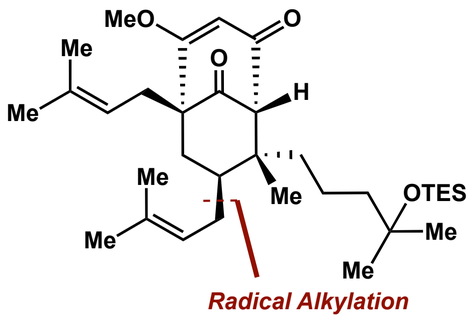

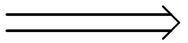

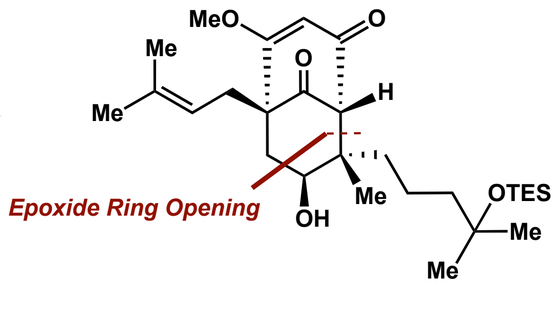

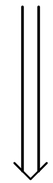

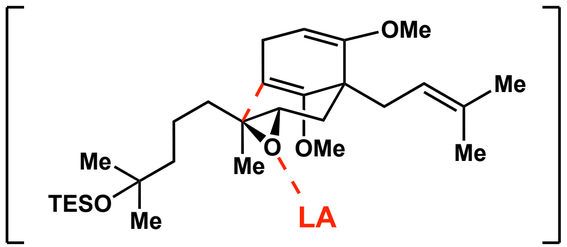

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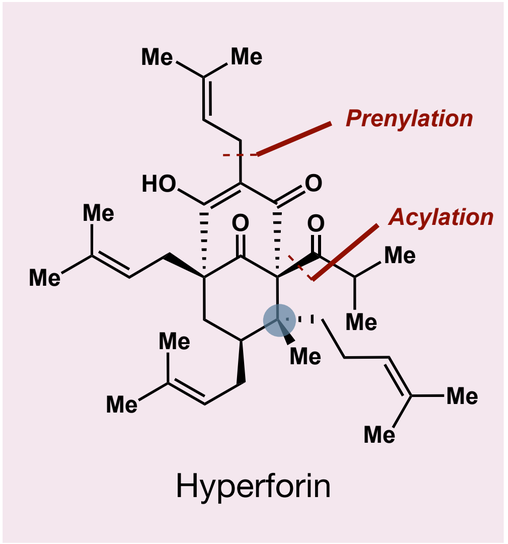

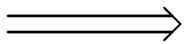

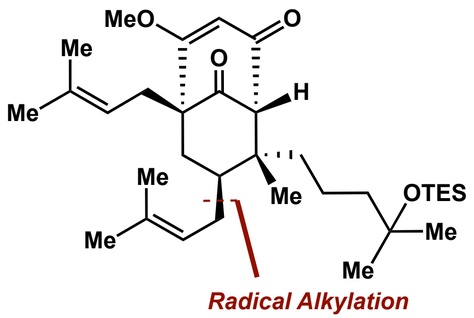

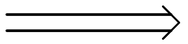

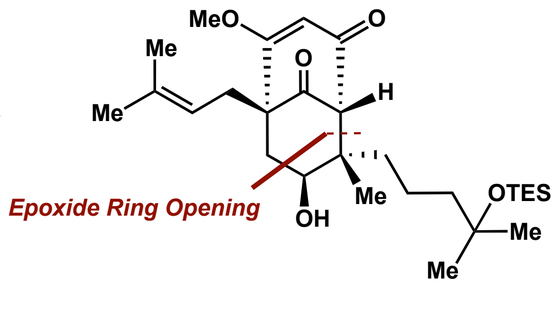

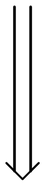

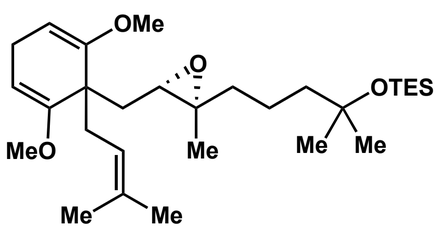

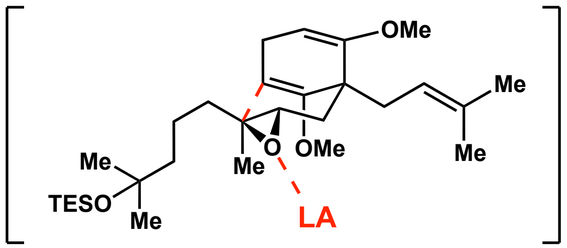

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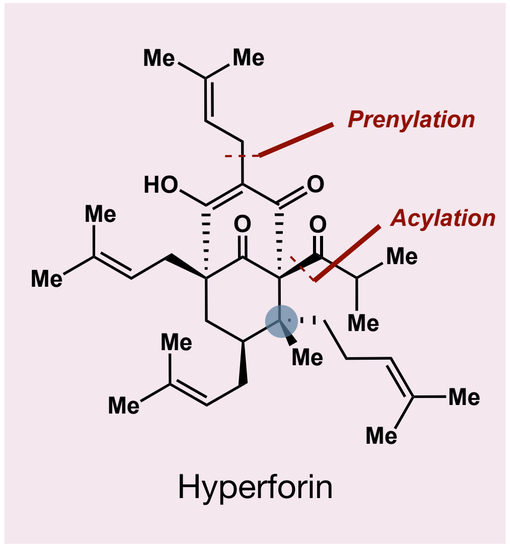
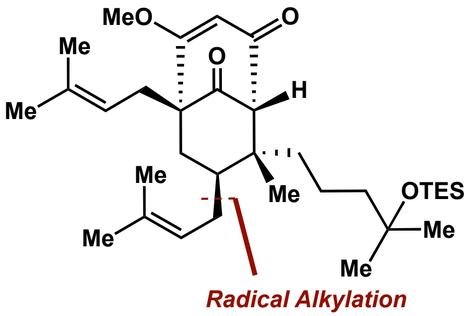
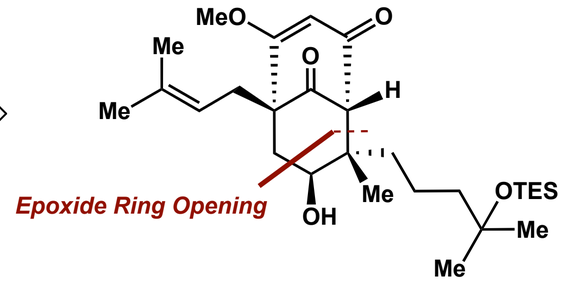
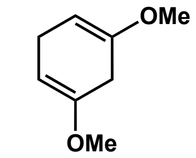
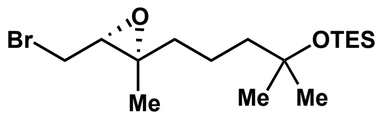
Total Synthesis of Hyperforin (Shair)

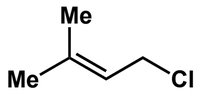


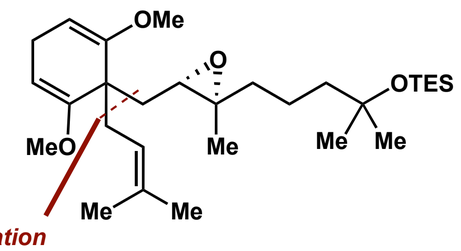


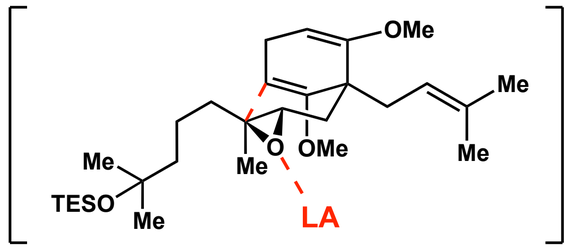












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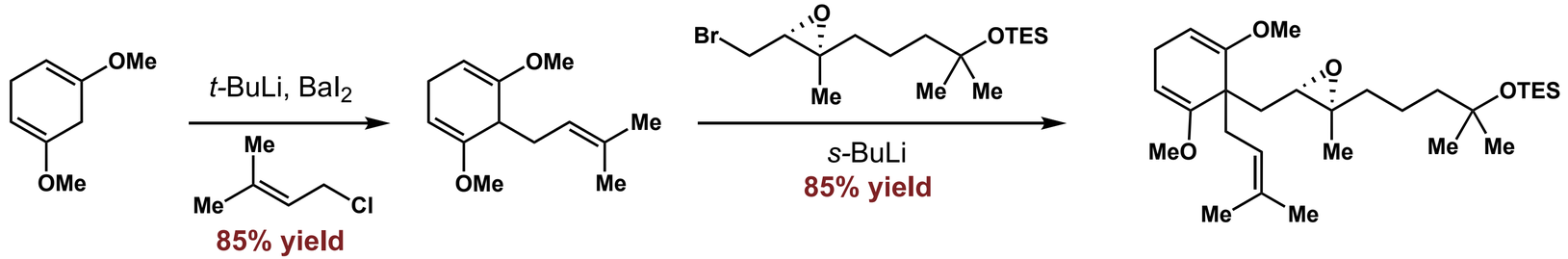
Total Synthesis of Hyperforin (Shair)



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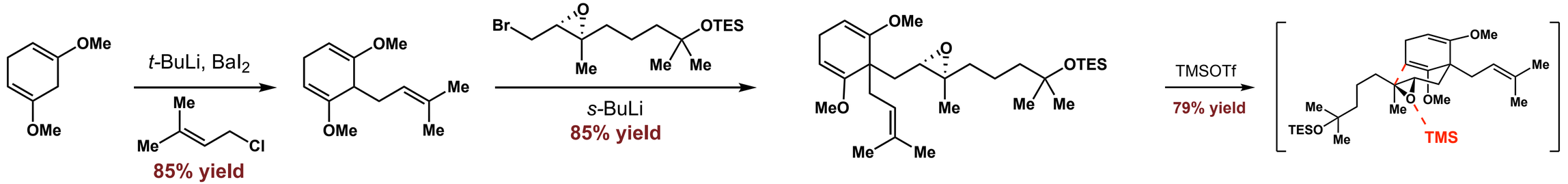

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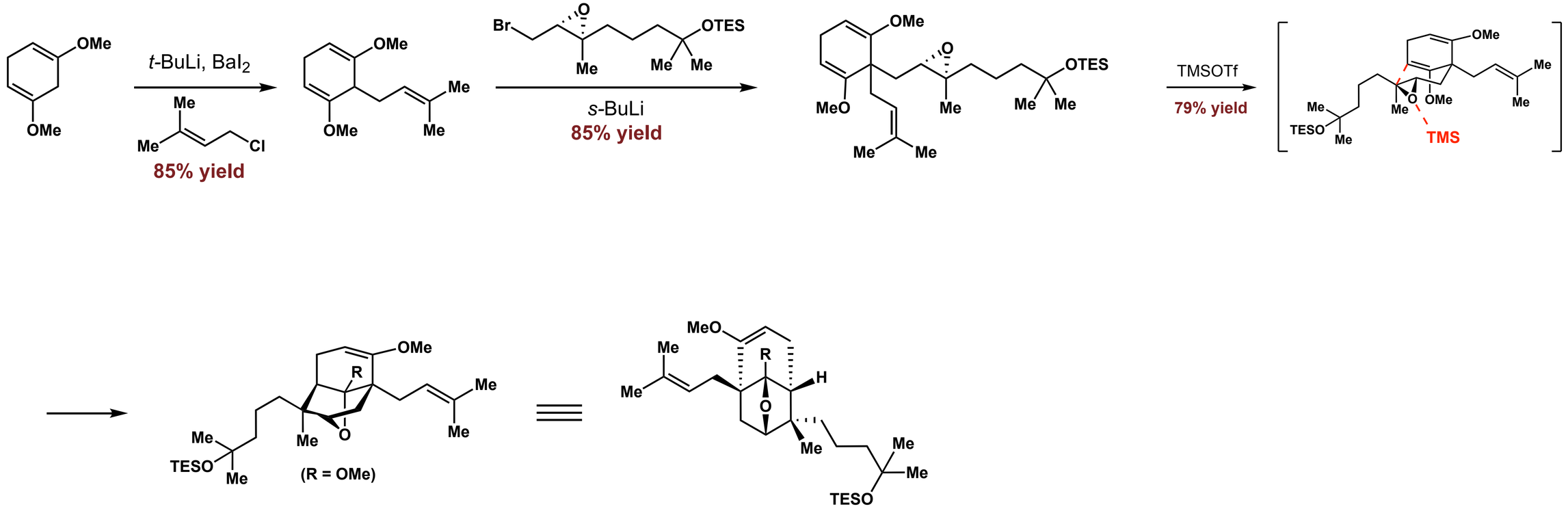

(>60 g prepared)

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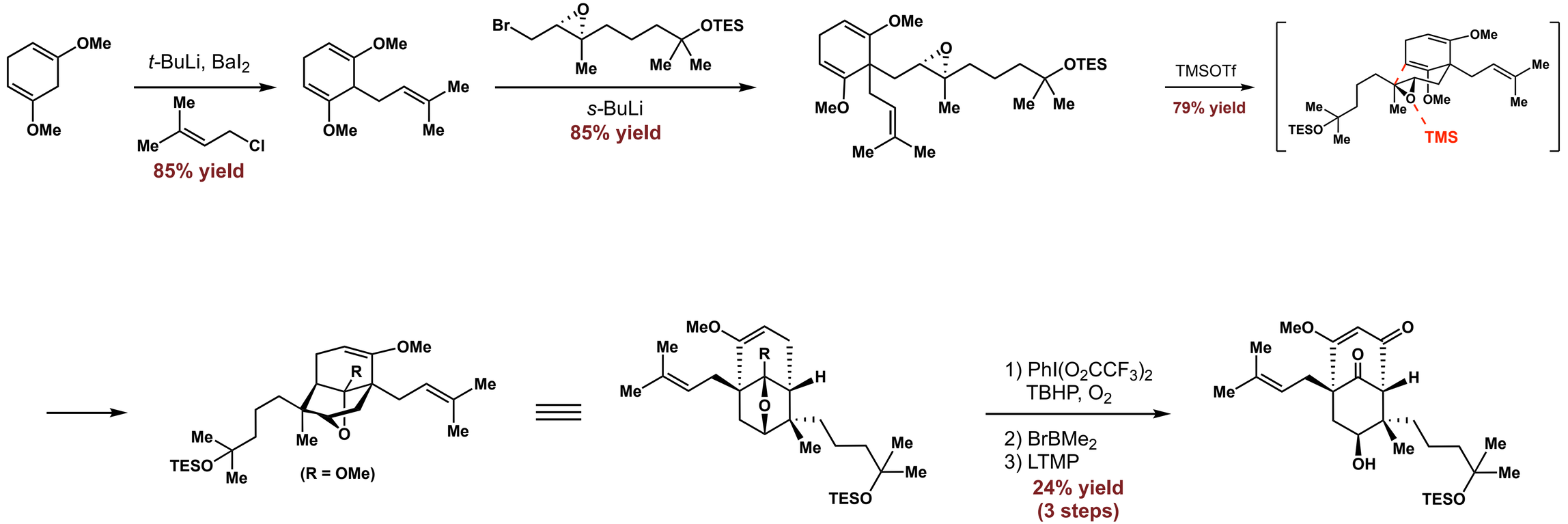

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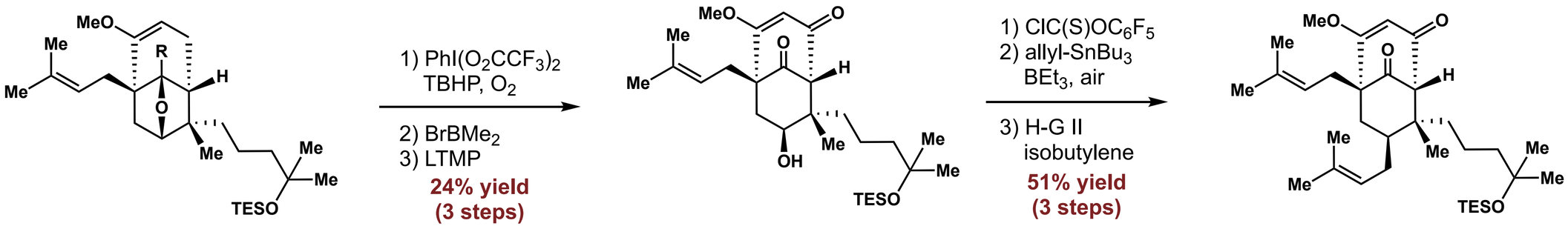

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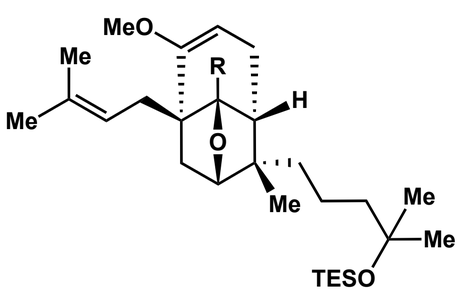
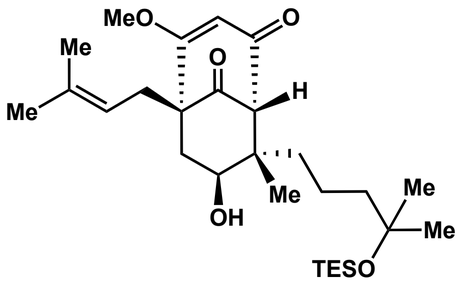


1) $PhI(O_2CCF_3)_2$
TBHP, O_2

2) $BrBMe_2$
3) LTMP

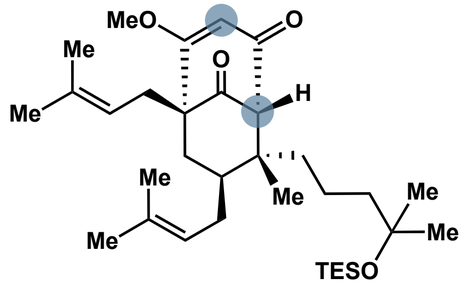
24% yield
(3 steps)

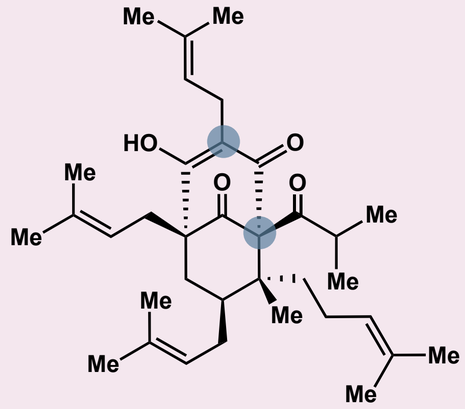


1) $ClC(S)OC_6F_5$
2) allyl-$SnBu_3$
BEt_3, air

3) H-G II
isobutylene

51% yield
(3 steps)





Hyperforin

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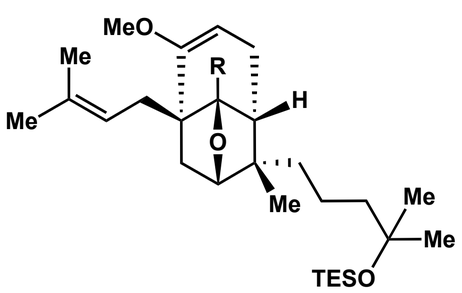

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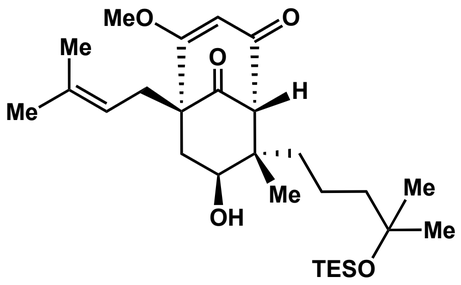

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51% yield
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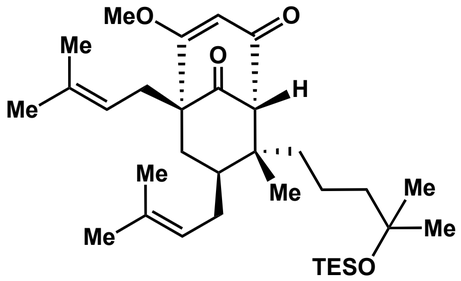
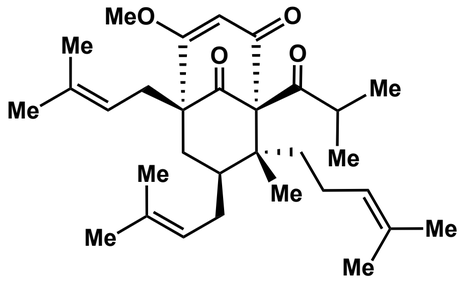
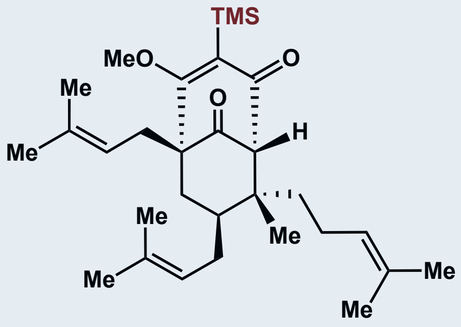


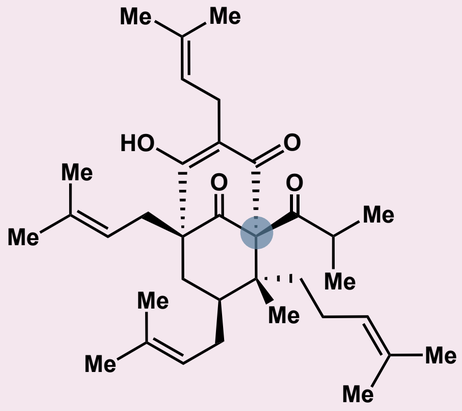
1) LTMP, TMSCl
2) LTMP, *i*PrCOCN

3) TsOH

29% yield
(3 steps)







Hyperforin

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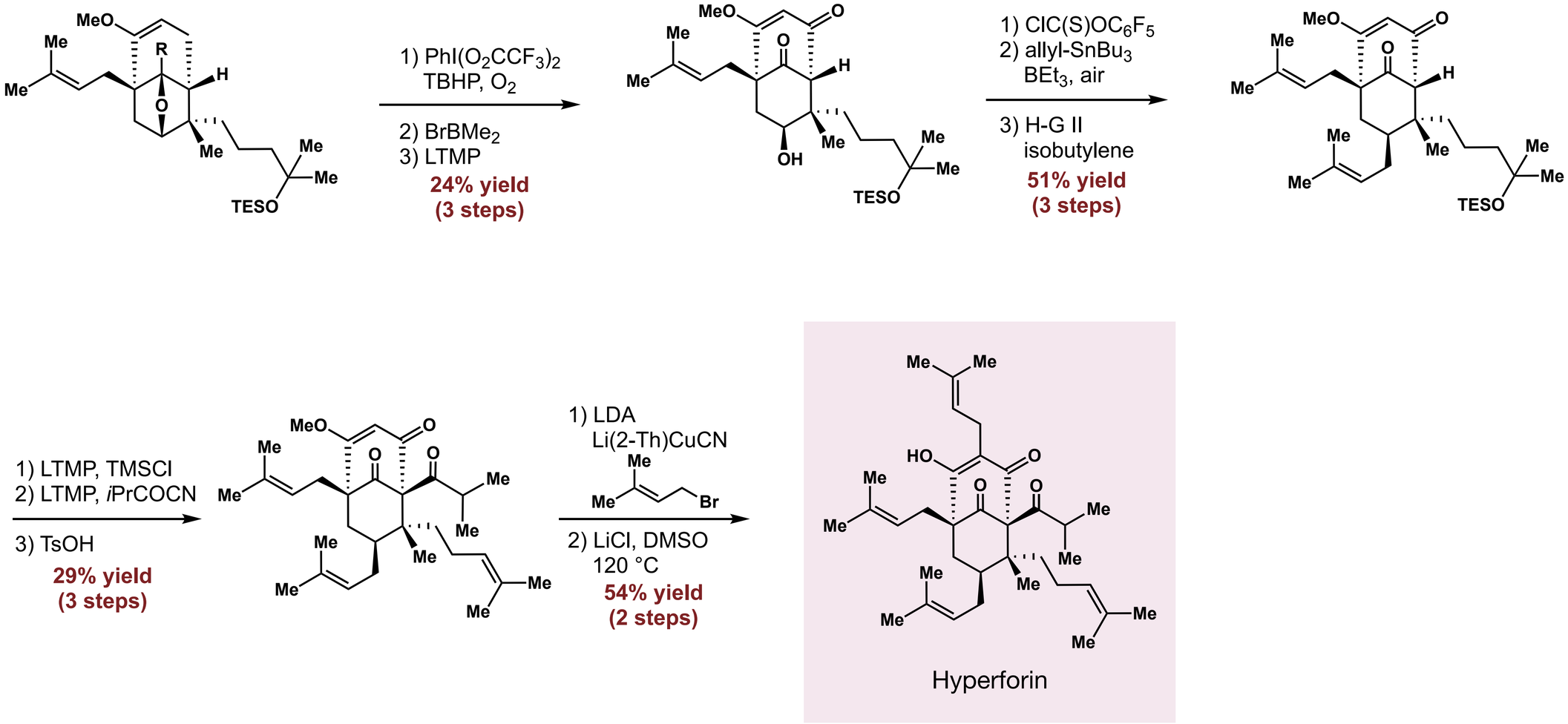
Total Synthesis of Hyperforin (Shair)



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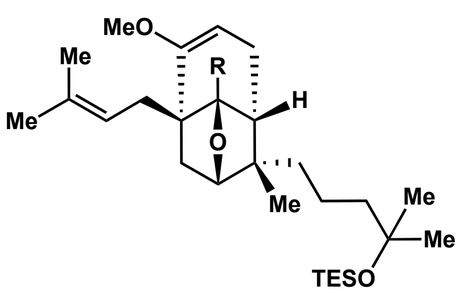

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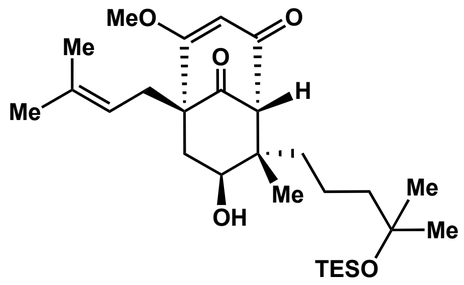

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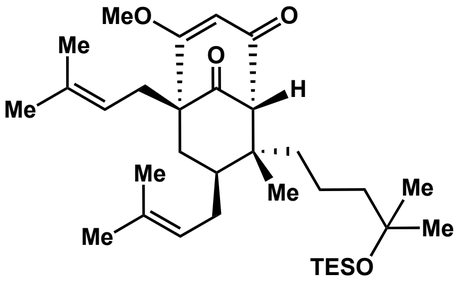

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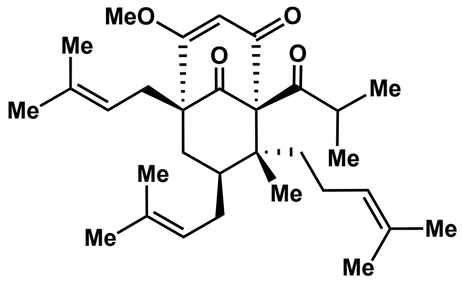
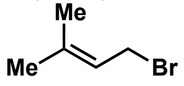
29% yield
(3 steps)

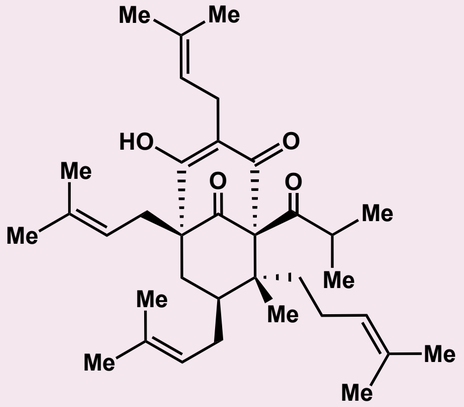


1) LDA
Li(2-Th)CuCN



2) LiCl, DMSO
120 °C

54% yield
(2 steps)



Hyperforin

Biomimetic cyclization

Enantioselective

18 steps LLS

Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644.

Total Synthesis of Hyperforin: A Quest of Synthetic Efficiency

1971: Isolation

2010: M. Shibasaki (**51 steps LLS**)

2013: M. Shair (**18 steps LLS**)

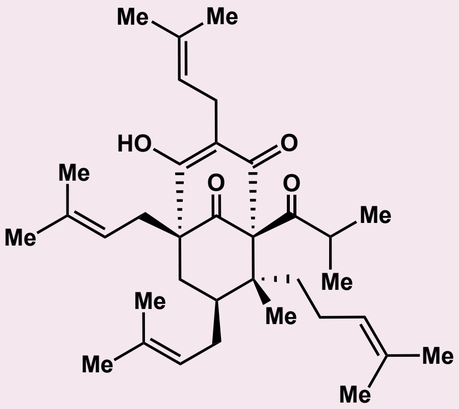
2015: T. Maimone (**10 steps LLS**)

2022: H. Li (**9 steps LLS**)

2014: L. Barriault (**17 steps LLS**)

1975: Structure Elucidation

2013: M. Nakada (**35 steps LLS**)

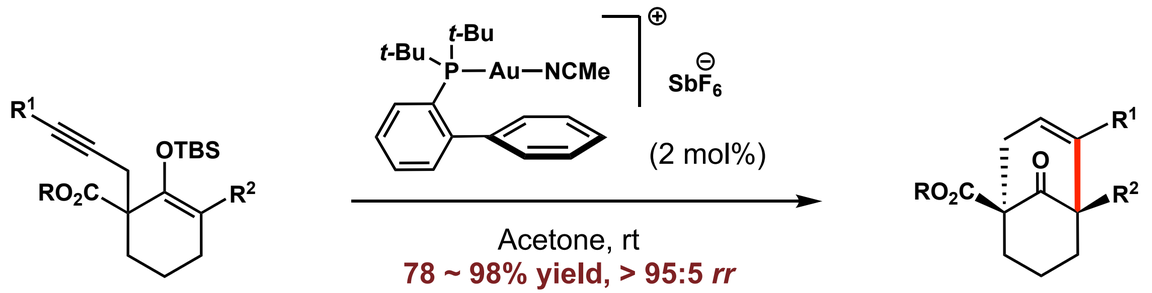


Hyperforin

Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103.
Uwamori, M.; Nakada, M. *Tetrahedron Lett.* **2013**, *54*, 2022.
Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644.
Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701.
Ting, C. P.; Maimone, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 10516.
Li, Y.; Hong, B.; Franzoni, I.; Wang, M.; Guan, W.; Jia, H.; Li, H. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116136.

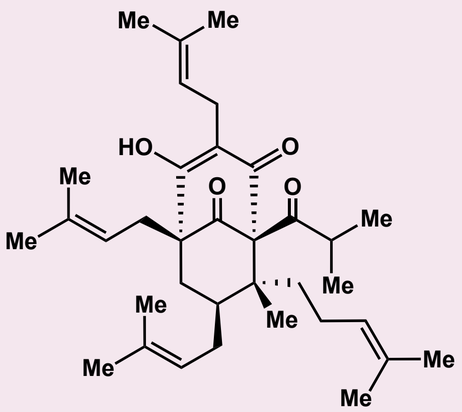
Total Synthesis of (±)-Hyperforin (Barriault)

Barriault (2009): Gold-Catalyzed Cyclization



R^1 = H, Me, Aryl, Br, I; R^2 = H, Me, Allyl

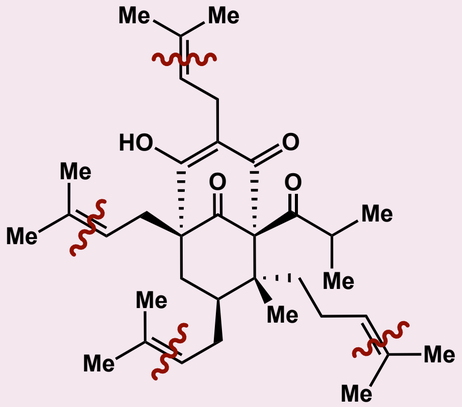
Barabé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *11*, 4236.



Hyperforin

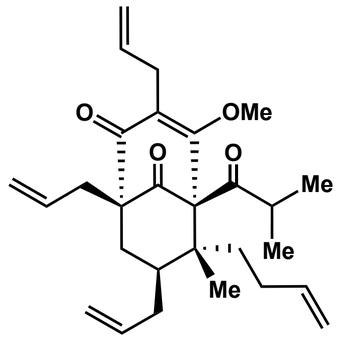
Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701.

Total Synthesis of (±)-Hyperforin (Barriault)



Hyperforin

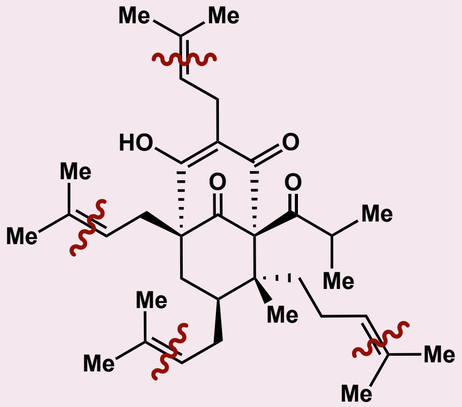
Global Cross Metathesis



(Nakada's intermediate)

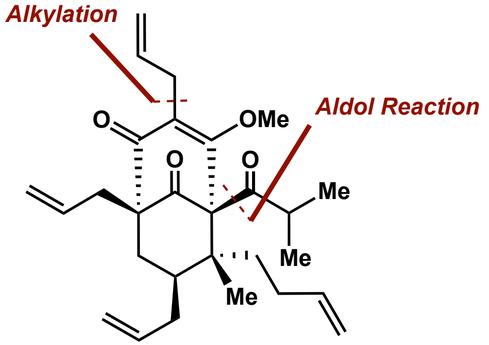
Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701.

Total Synthesis of (±)-Hyperforin (Barriault)

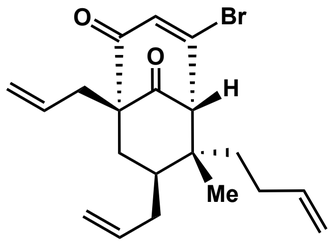


Hyperforin

Global Cross Metathesis

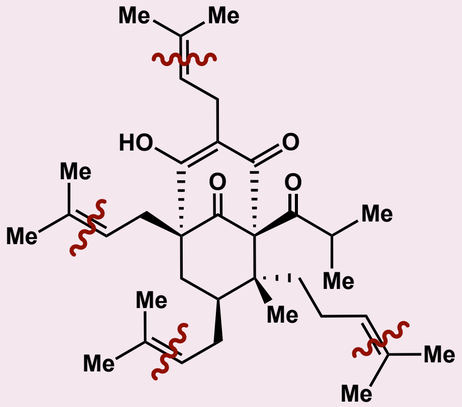


(Nakada's intermediate)



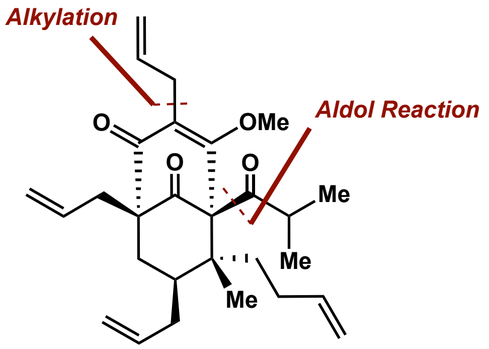
Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701.

Total Synthesis of (±)-Hyperforin (Barriault)

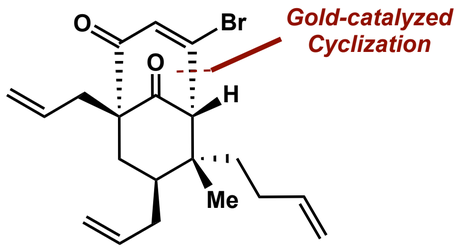


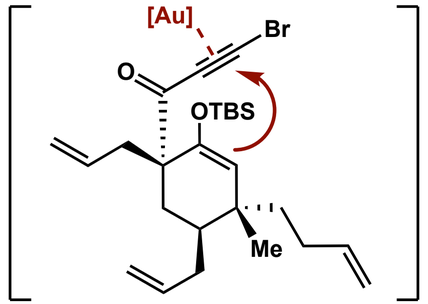
Hyperforin

Global Cross Metathesis



(Nakada's intermediate)





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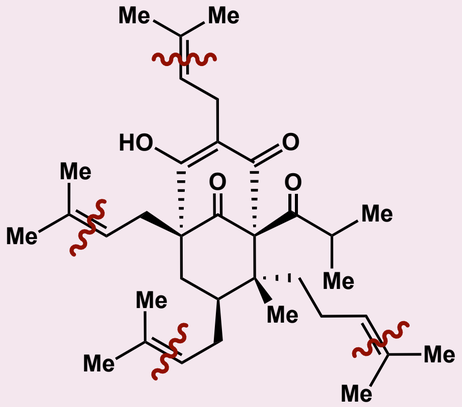
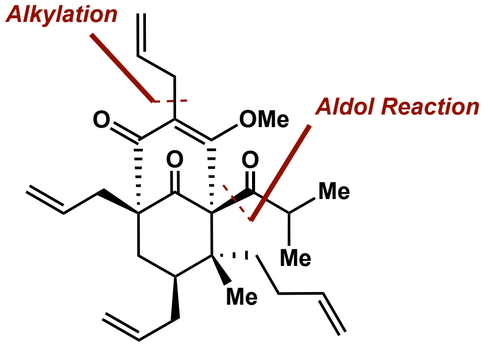
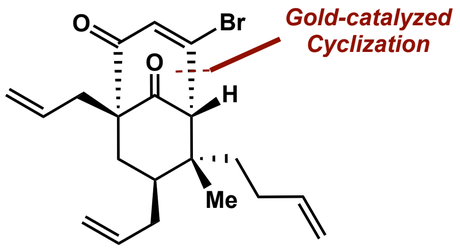


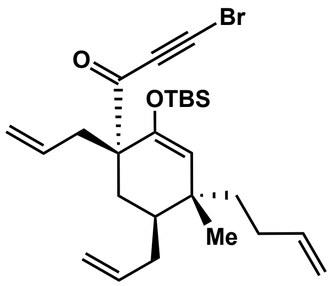
Hyperforin

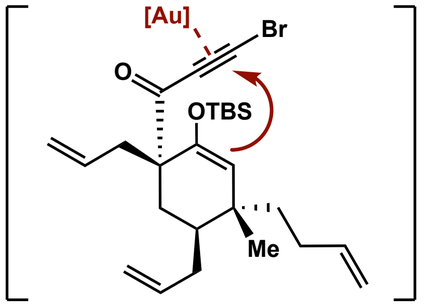
Global Cross Metathesis



(Nakada's intermediate)







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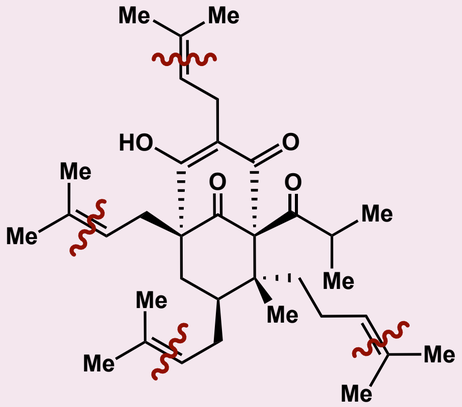
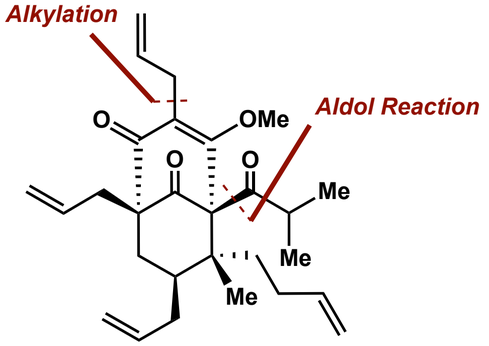
Total Synthesis of (±)-Hyperforin (Barriault)

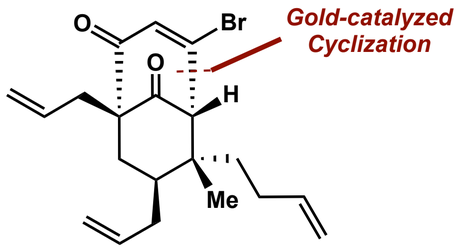


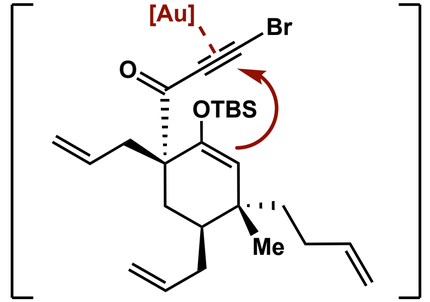
Hyperforin

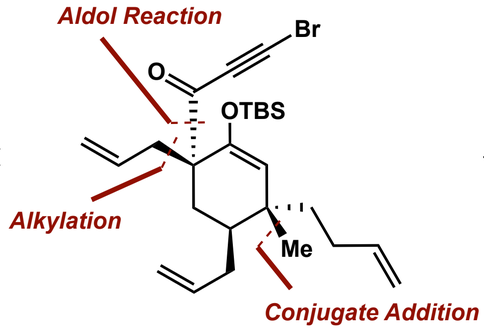
Global Cross Metathesis

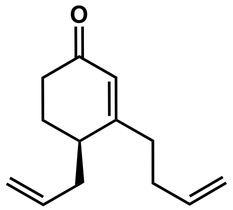


(Nakada's intermediate)









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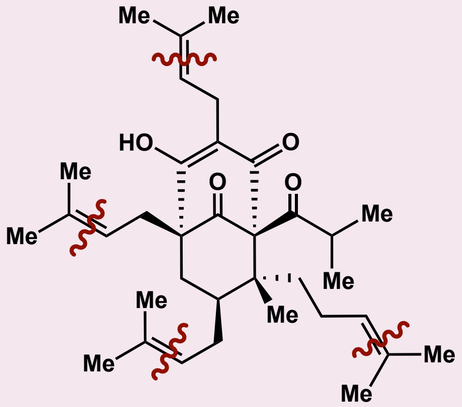
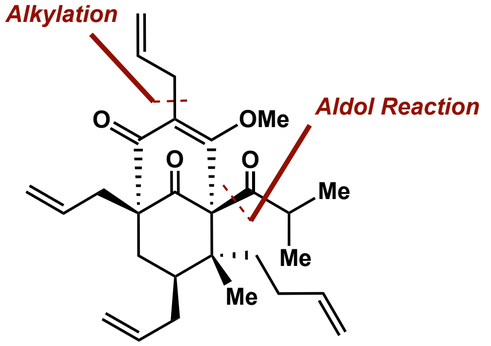
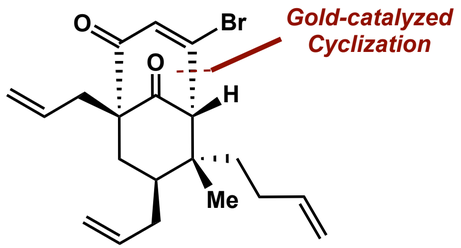


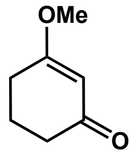
Hyperforin

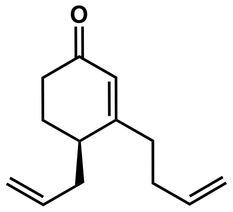
Global Cross Metathesis

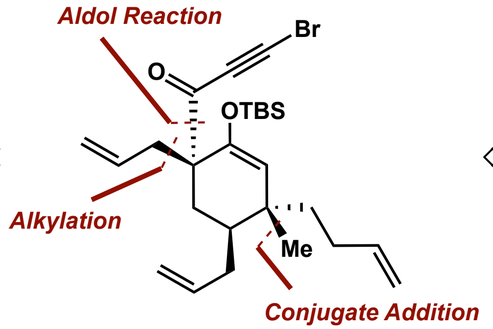


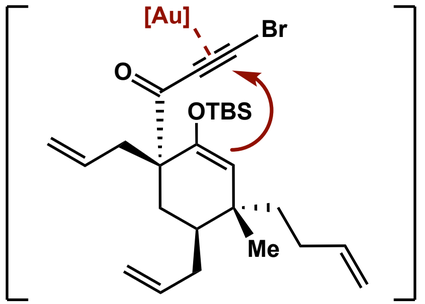
(Nakada's intermediate)





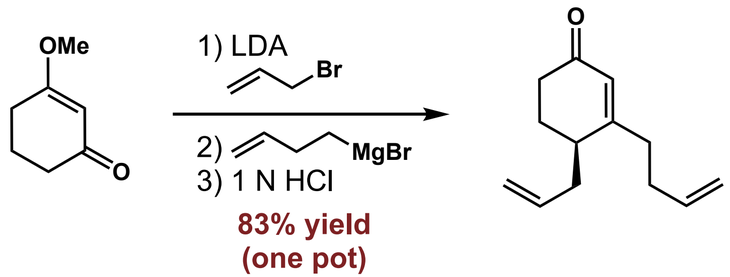






Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701.

Total Synthesis of (±)-Hyperforin (Barriault)



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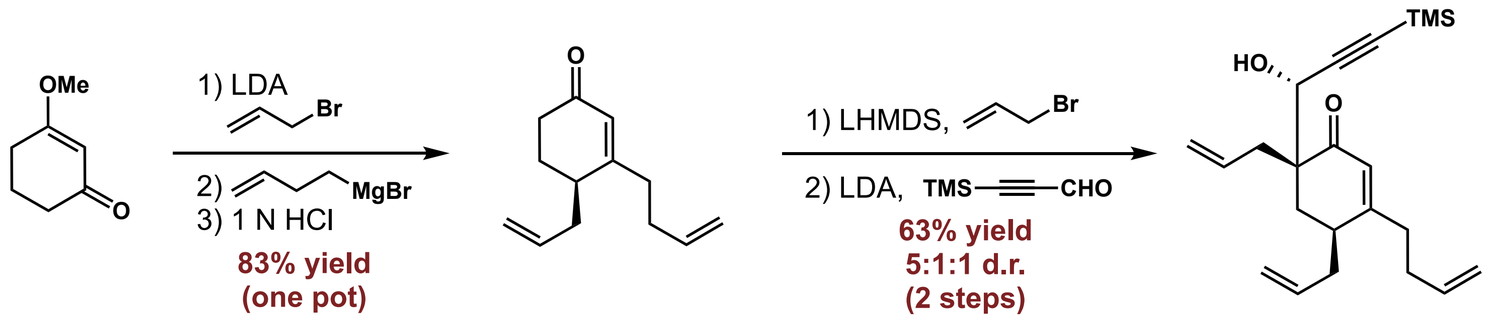

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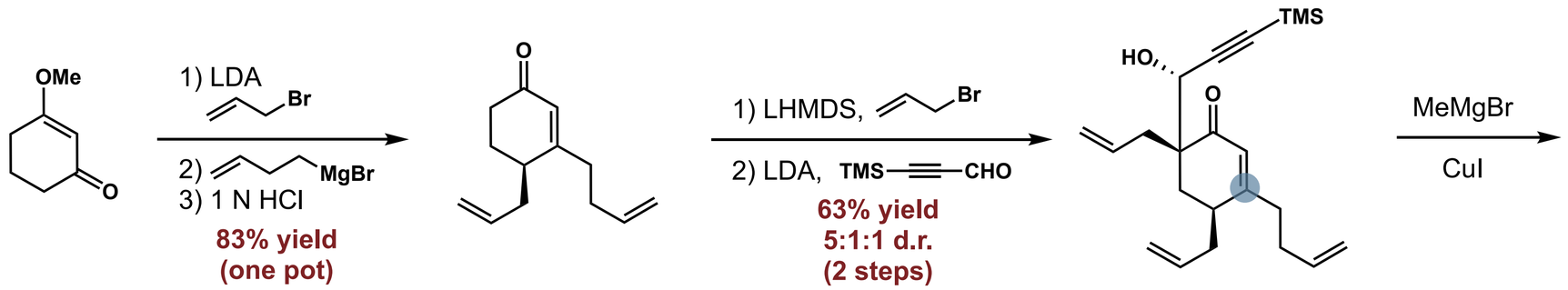

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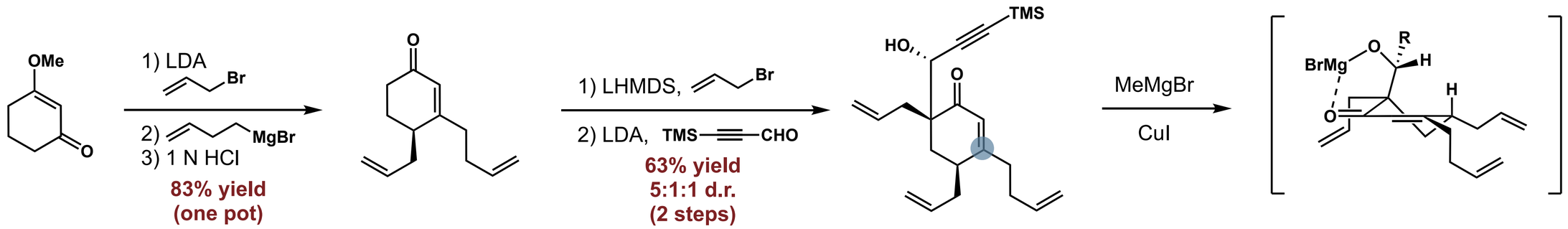

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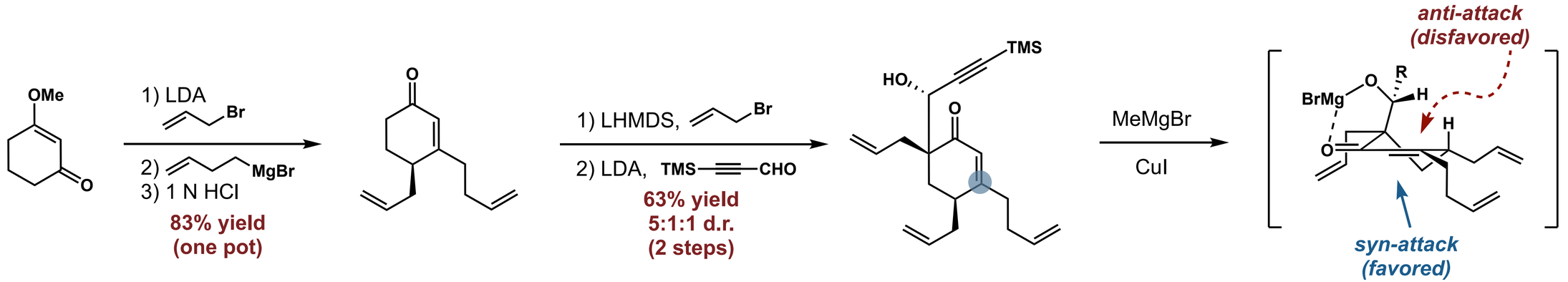

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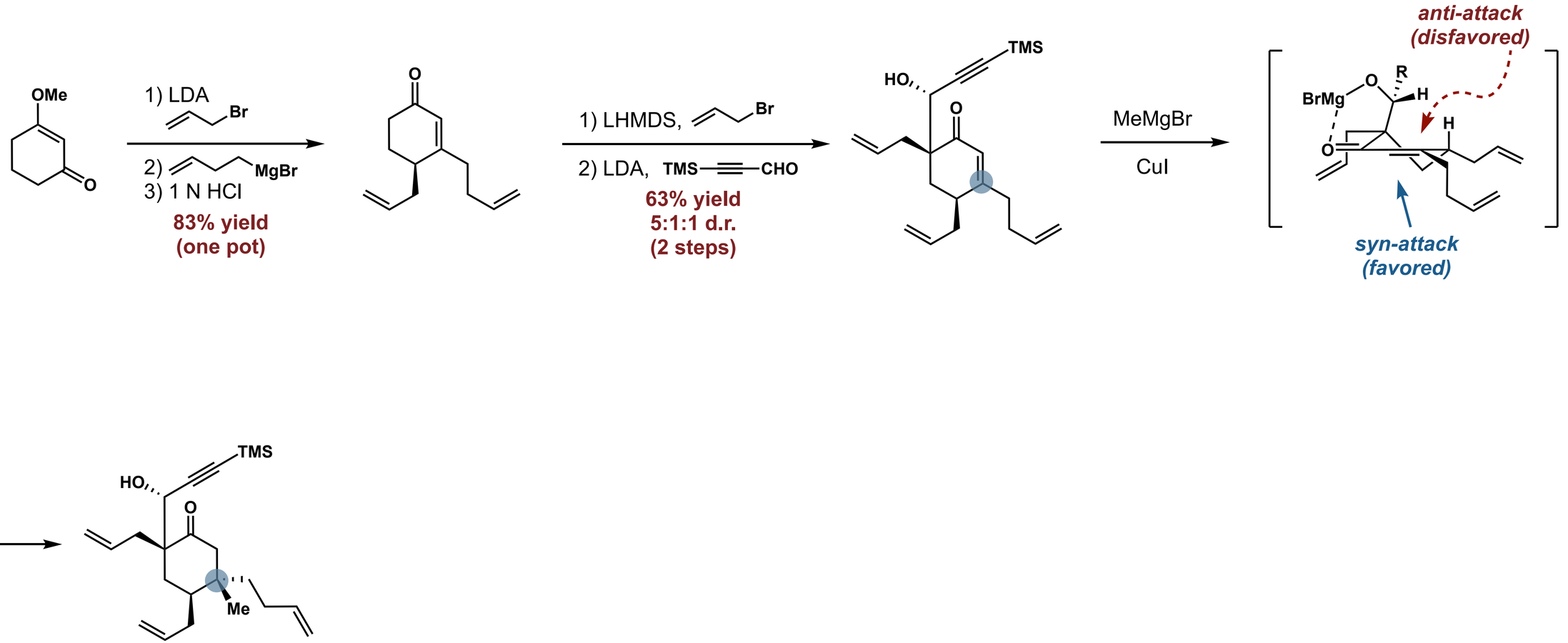

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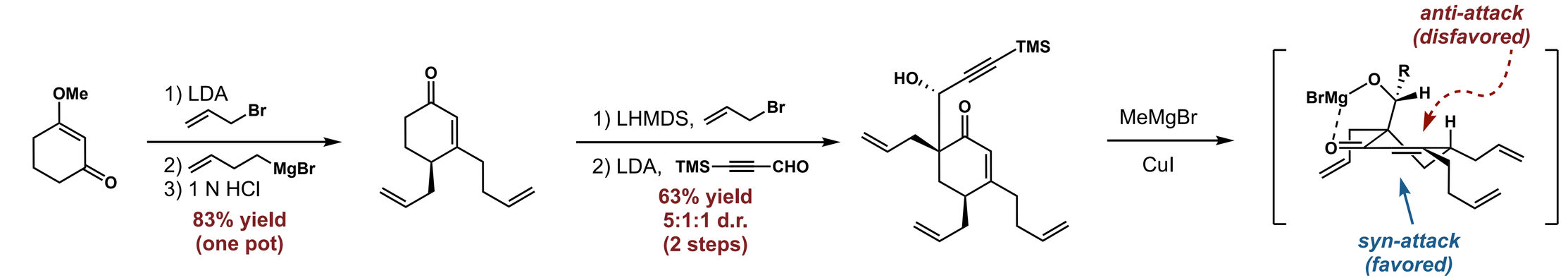

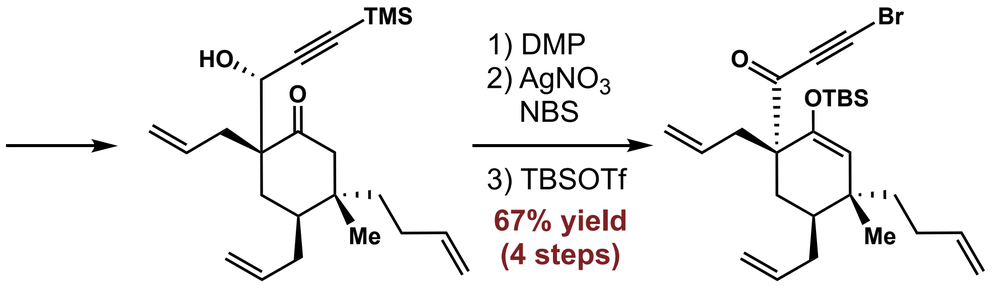

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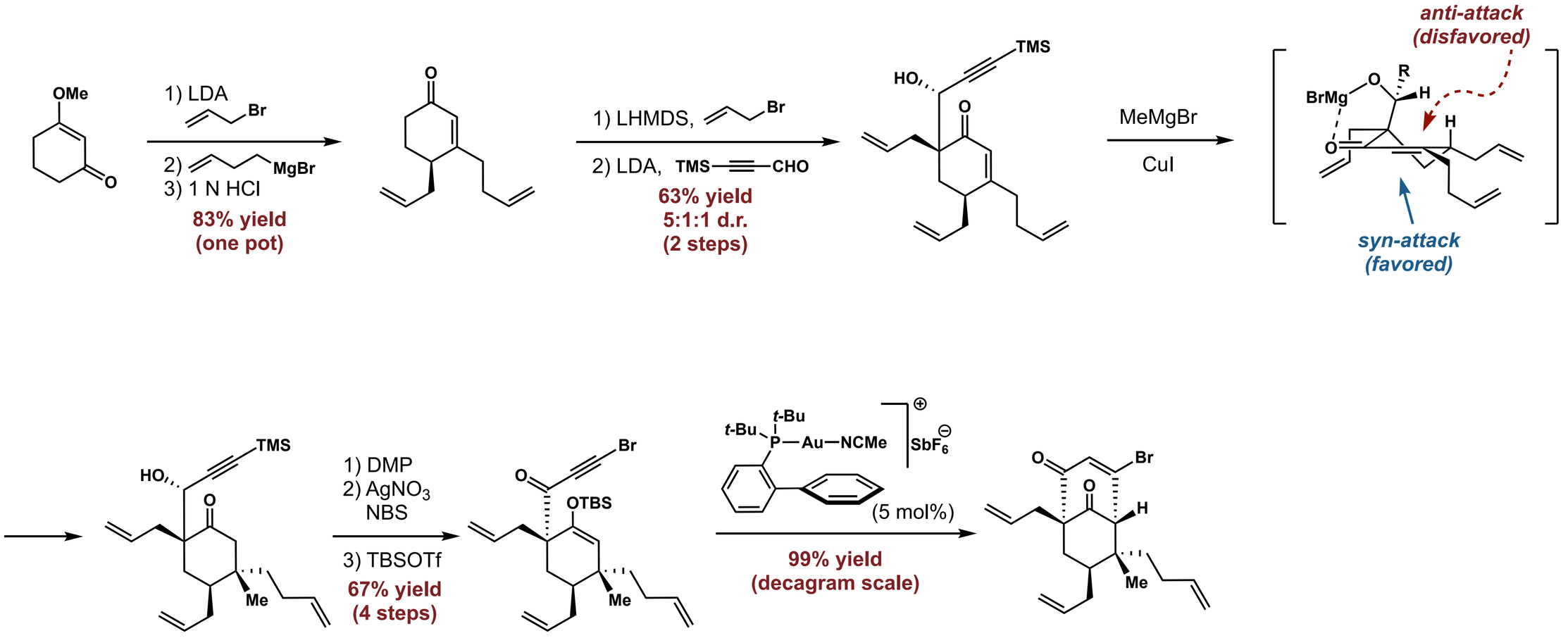

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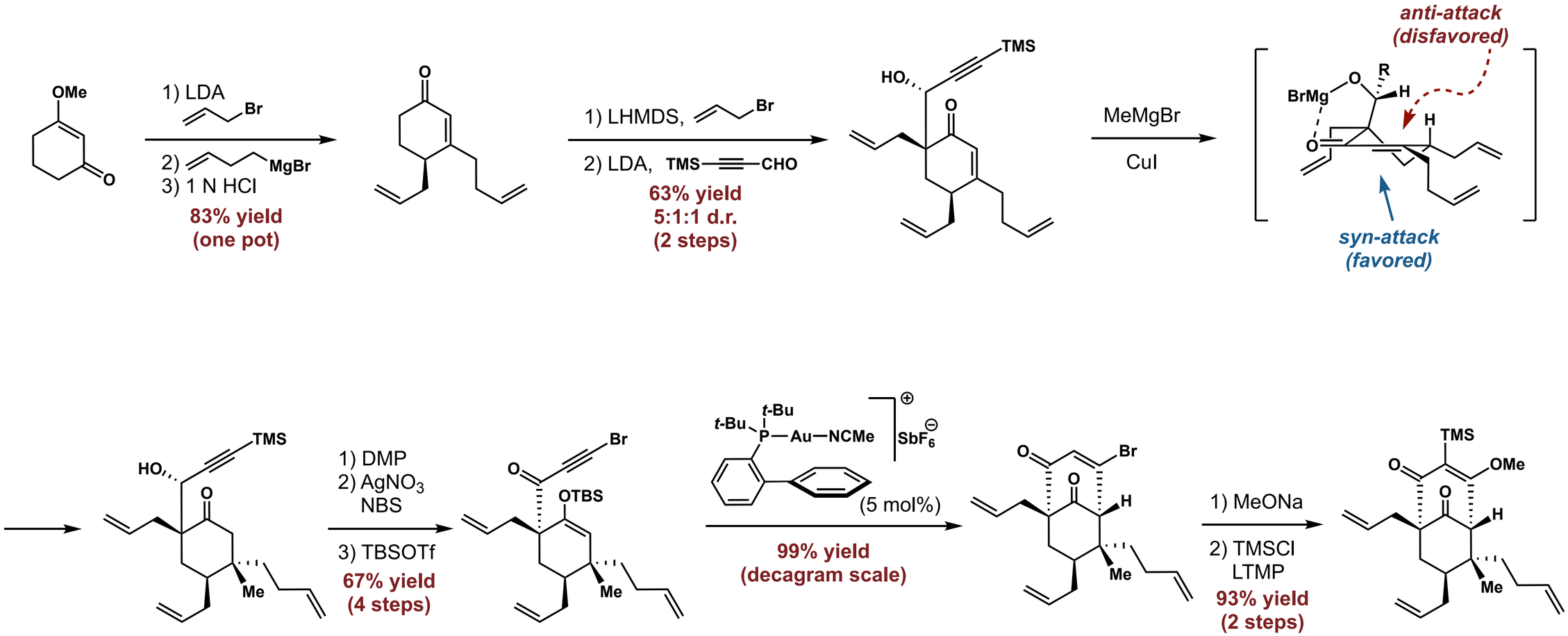

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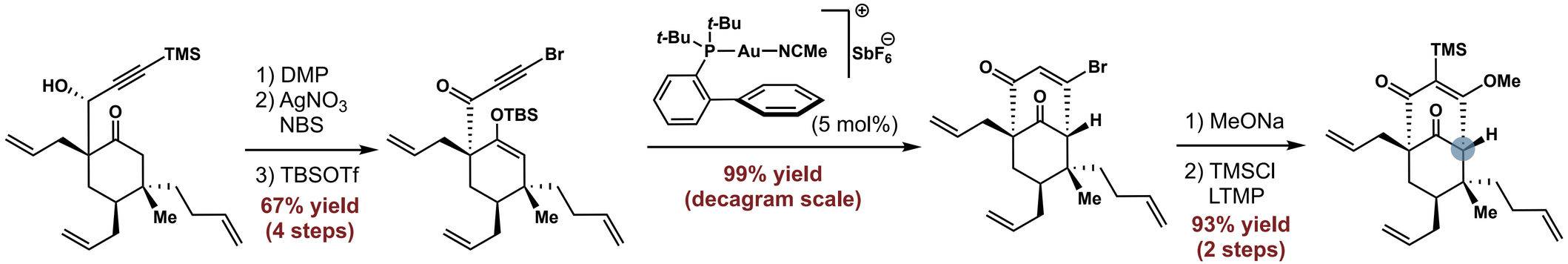

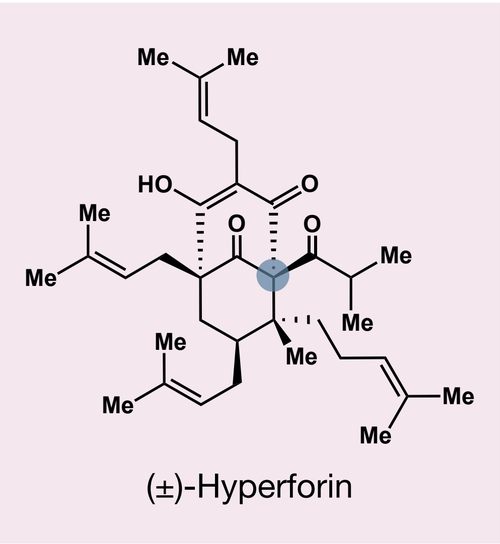

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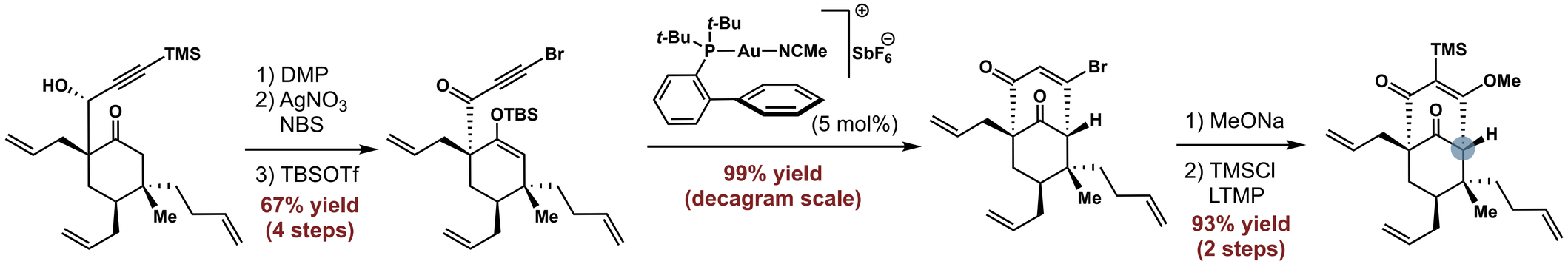
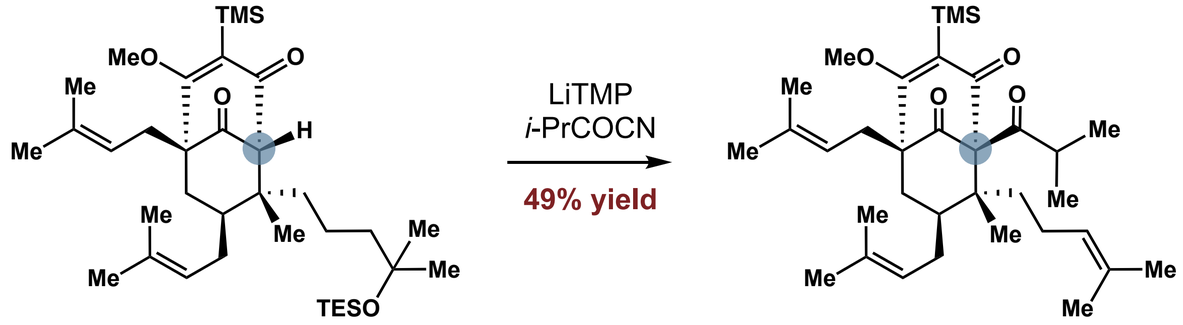
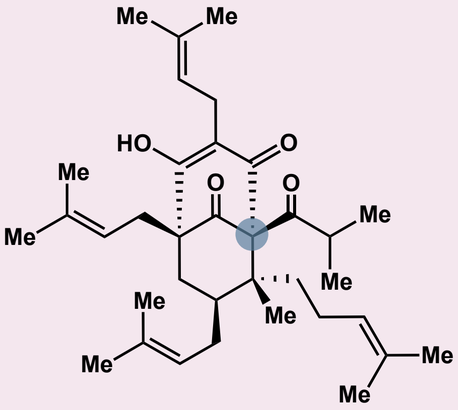


Shair (2013): Bridgehead Acylation



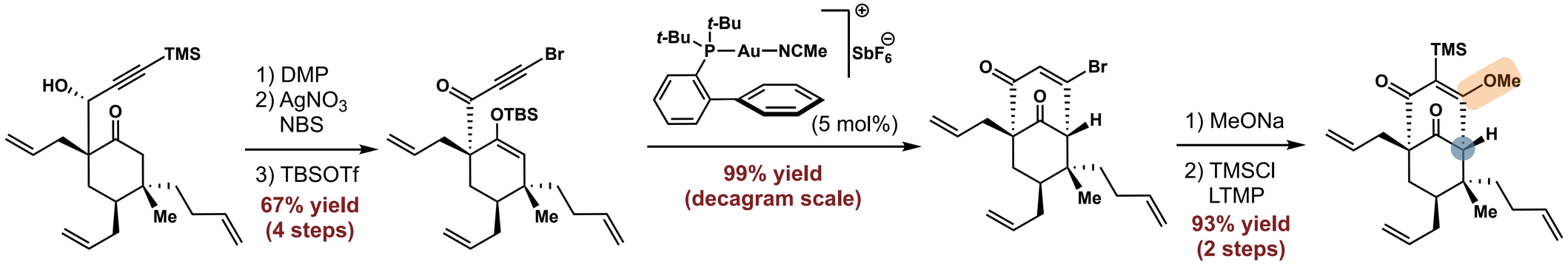
Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644.



(±)-Hyperforin

Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701.

Total Synthesis of (±)-Hyperforin (Barriault)



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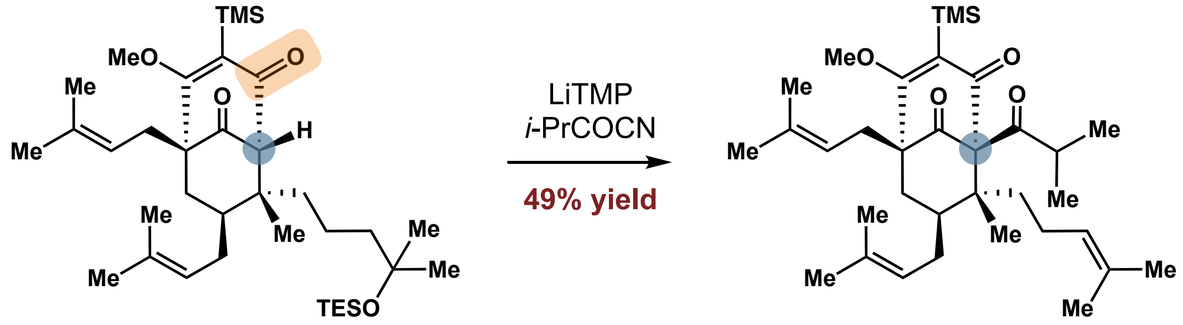
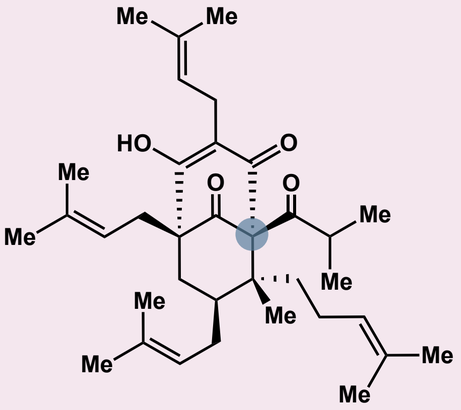


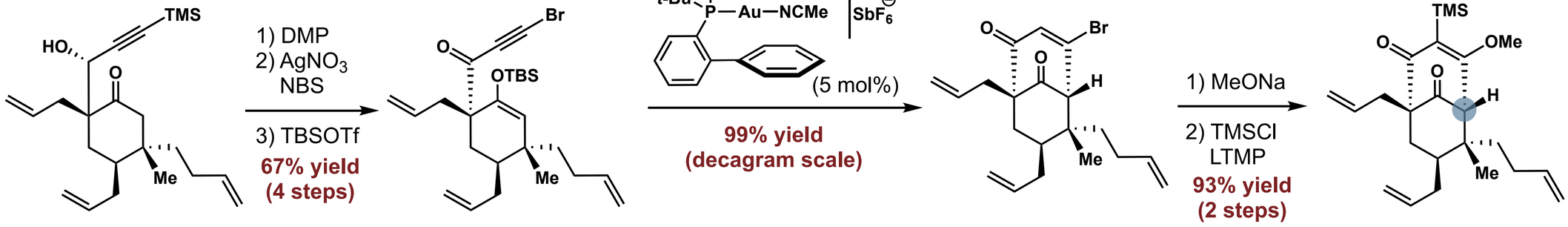
Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644.

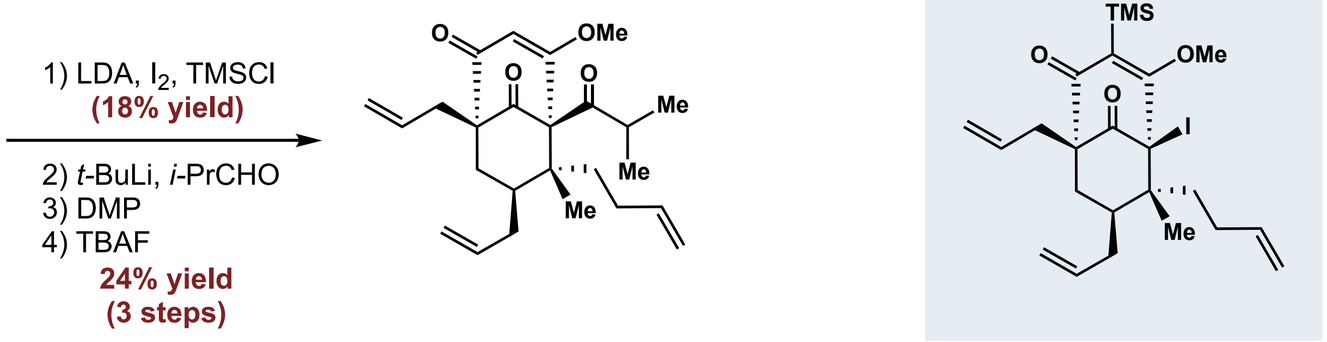


(±)-Hyperforin

Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701.

Total Synthesis of (±)-Hyperforin (Barriault)





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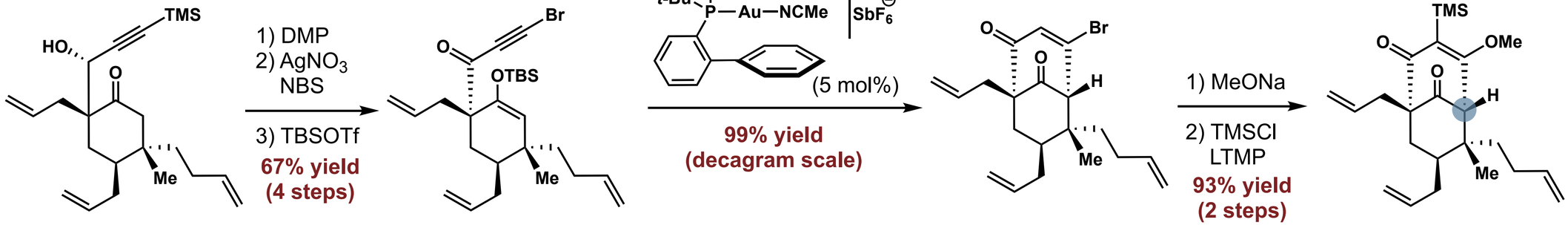

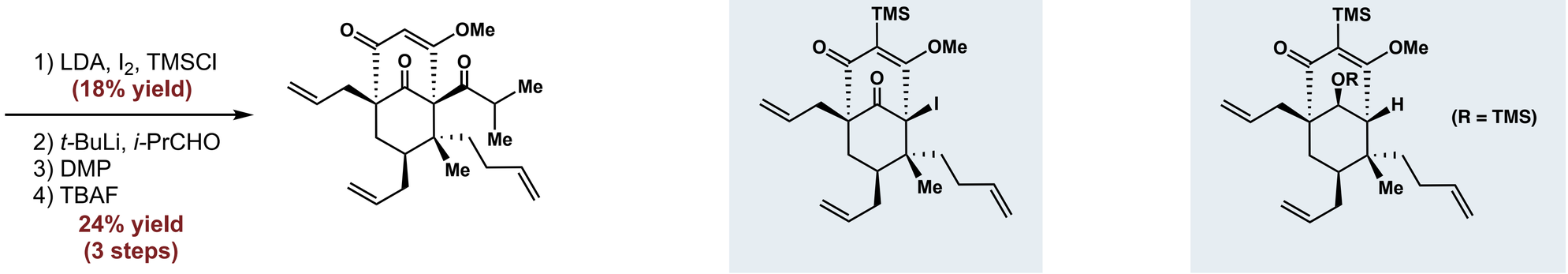

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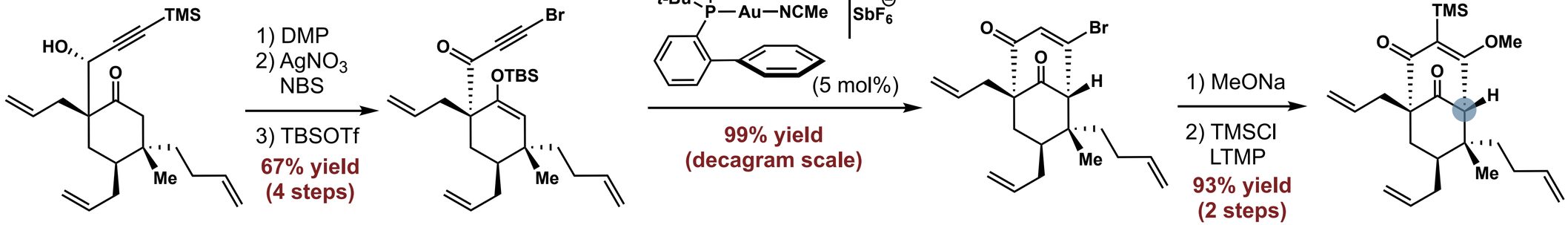

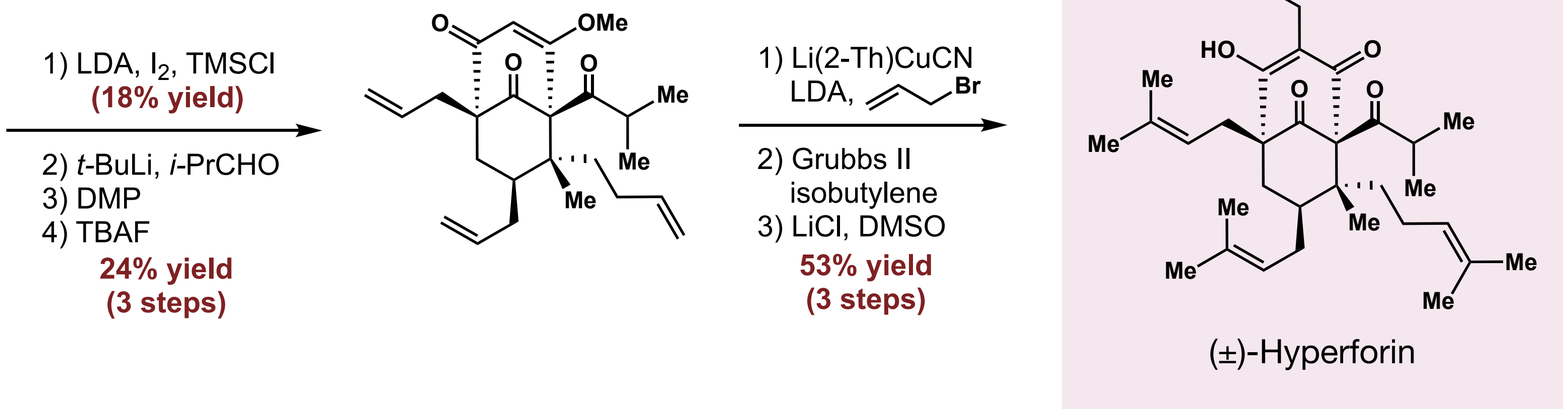

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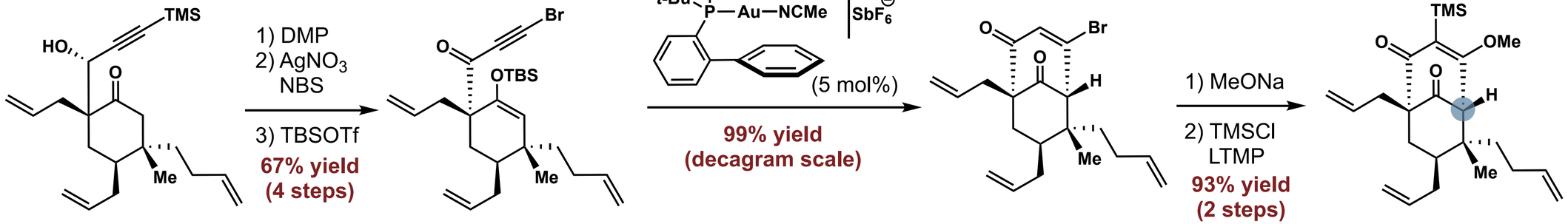

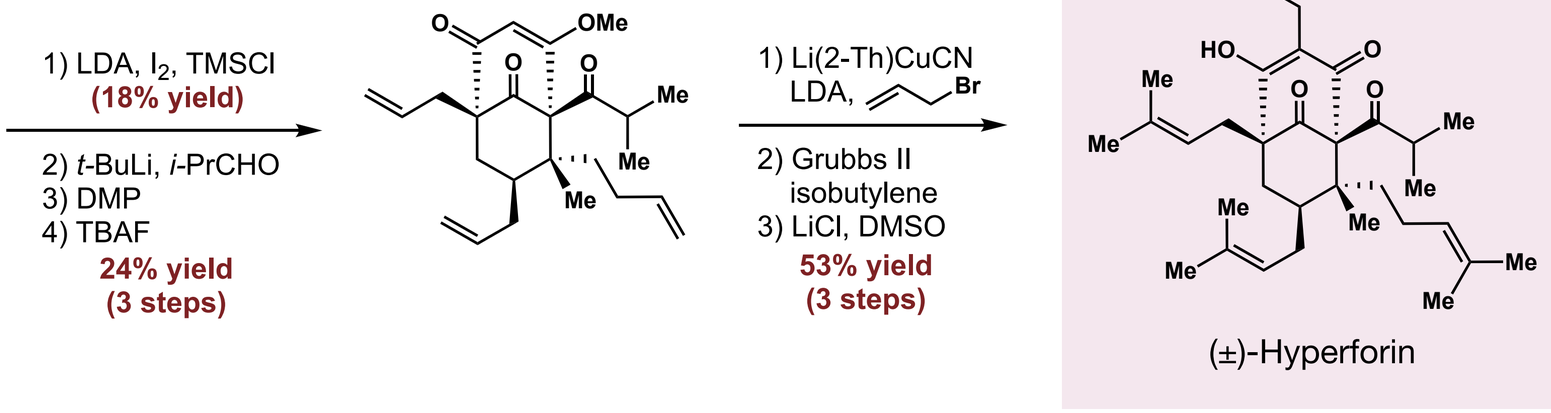

Global cross metathesis

Efficient gold-catalysis

17 steps LLS

Poor bridgehead acylation
Racemic synthesis

Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701.

Total Synthesis of Hyperforin: A Quest of Synthetic Efficiency

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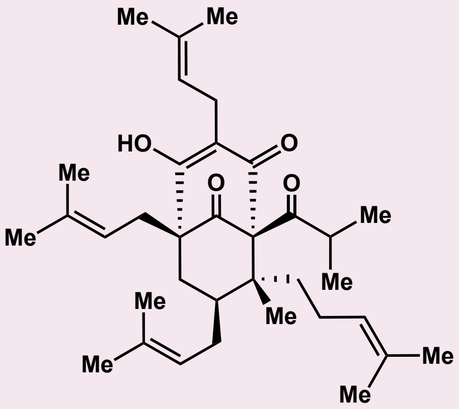

Hyperforin

Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103.
Uwamori, M.; Nakada, M. *Tetrahedron Lett.* **2013**, *54*, 2022.
Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644.
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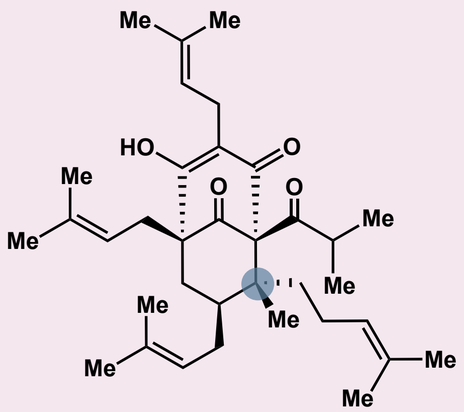
Ting, C. P.; Maimone, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 10516.
Li, Y.; Hong, B.; Franzoni, I.; Wang, M.; Guan, W.; Jia, H.; Li, H. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116136.

Total Synthesis of (±)-Hyperforin (Maimone)



Hyperforin

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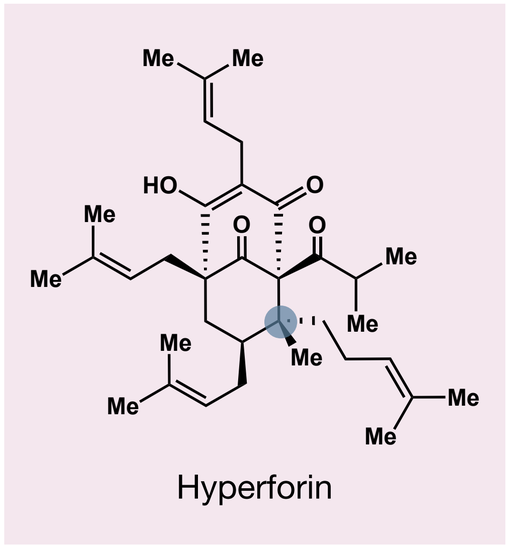

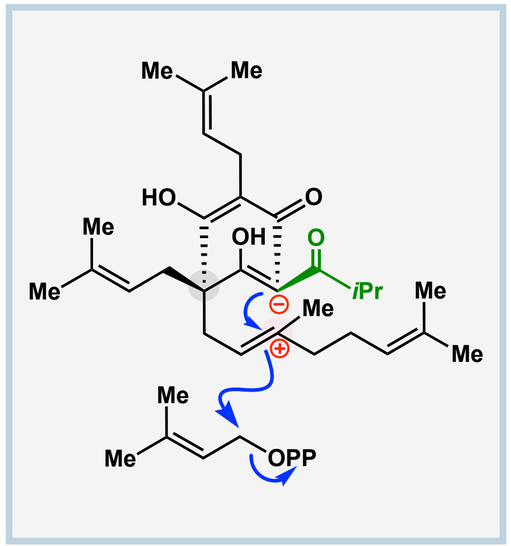

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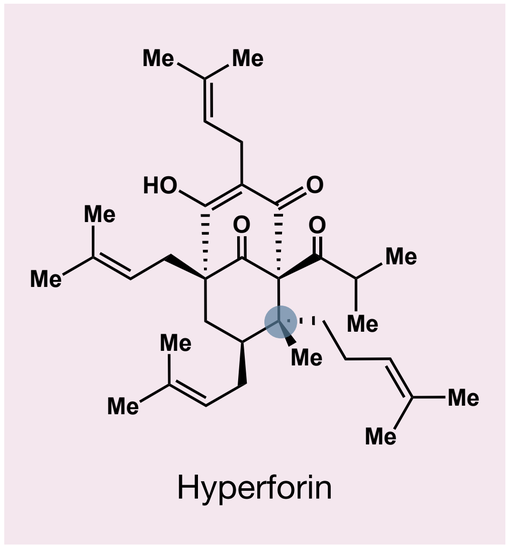
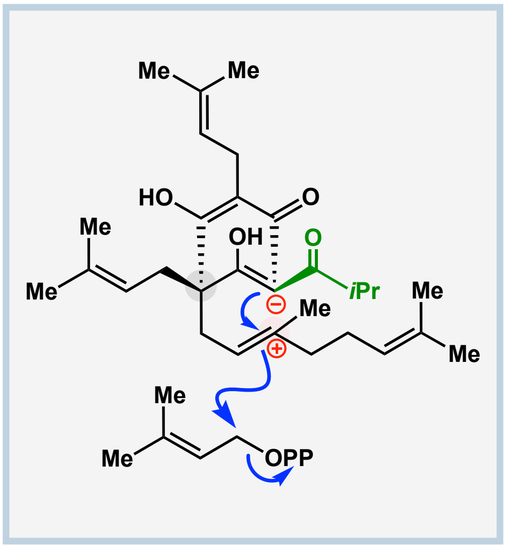
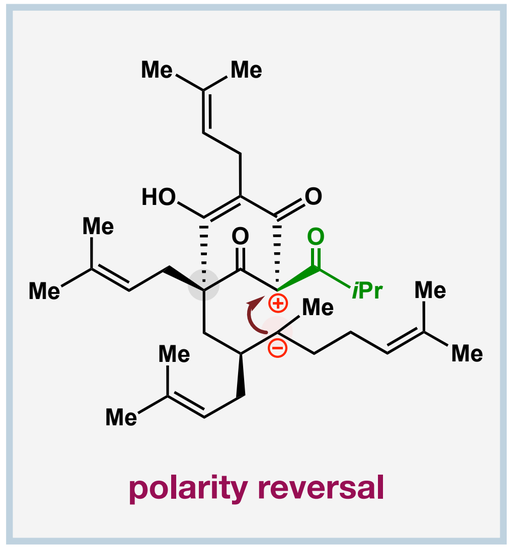


Hyperforin





polarity reversal

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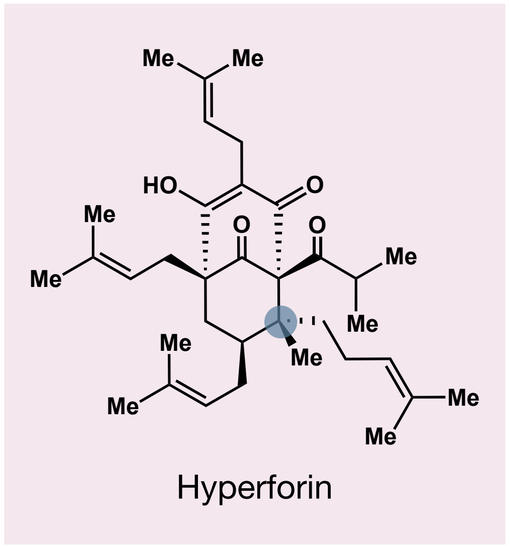

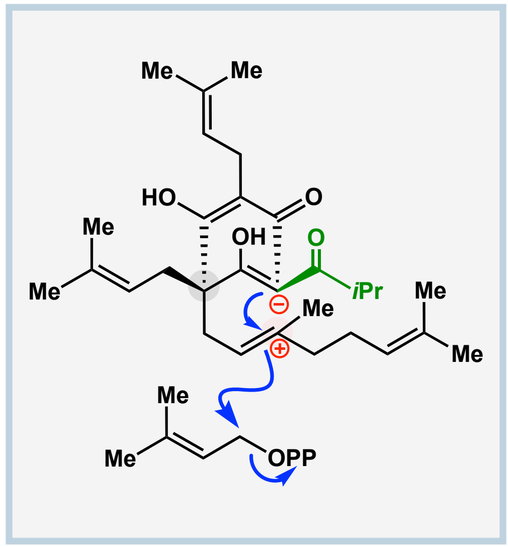

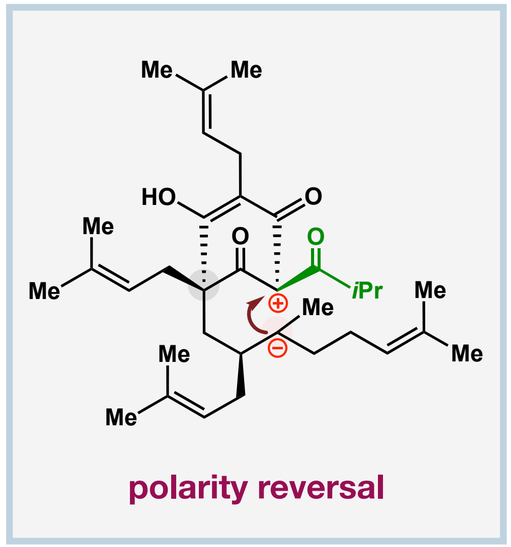

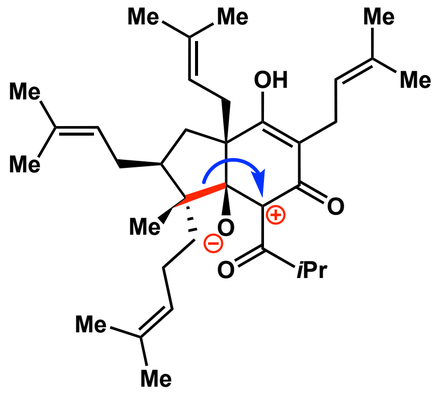

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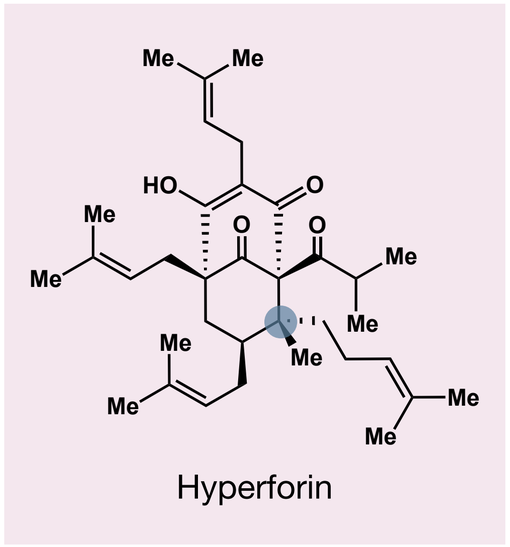
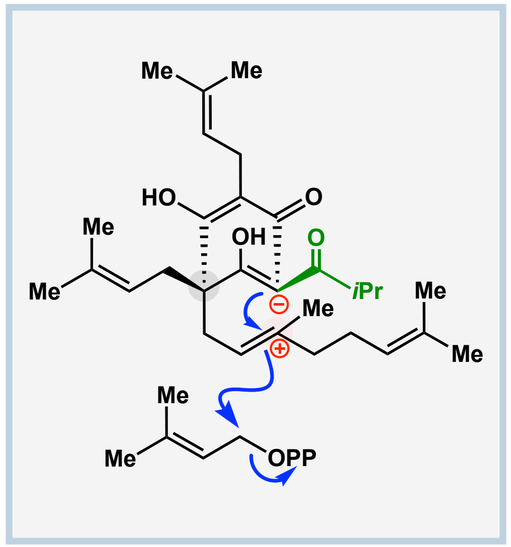
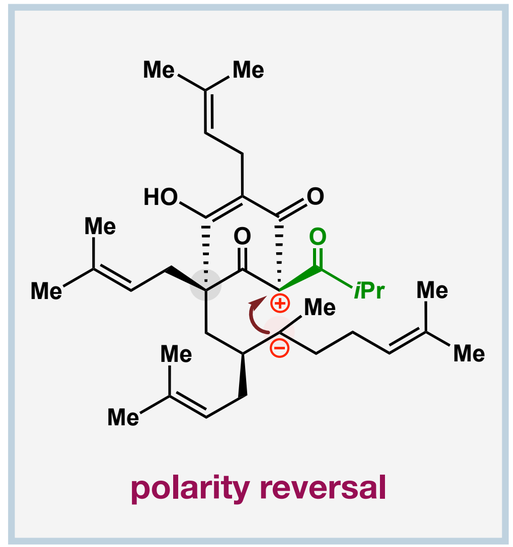
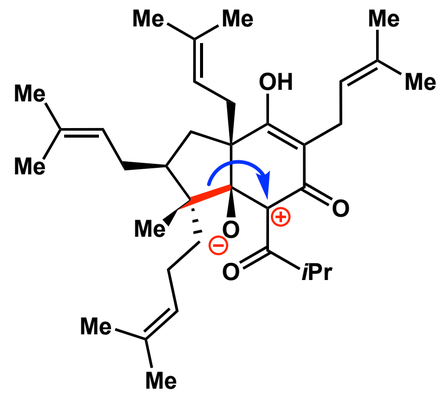
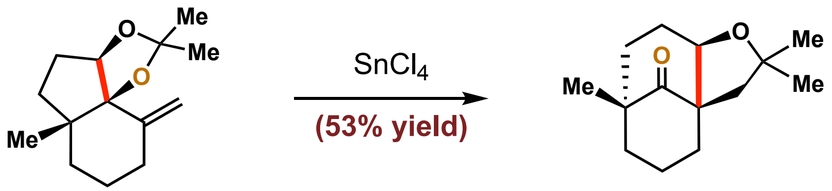








Barriault (2005): Tandem Prins/Semi-pinacol Rearrangement



Lavigne, R. M. A.; Riou, M.; Girardin, M.; Morency, L.; Barriault, L. *Org. Lett.* **2005**, *7*, 5921.

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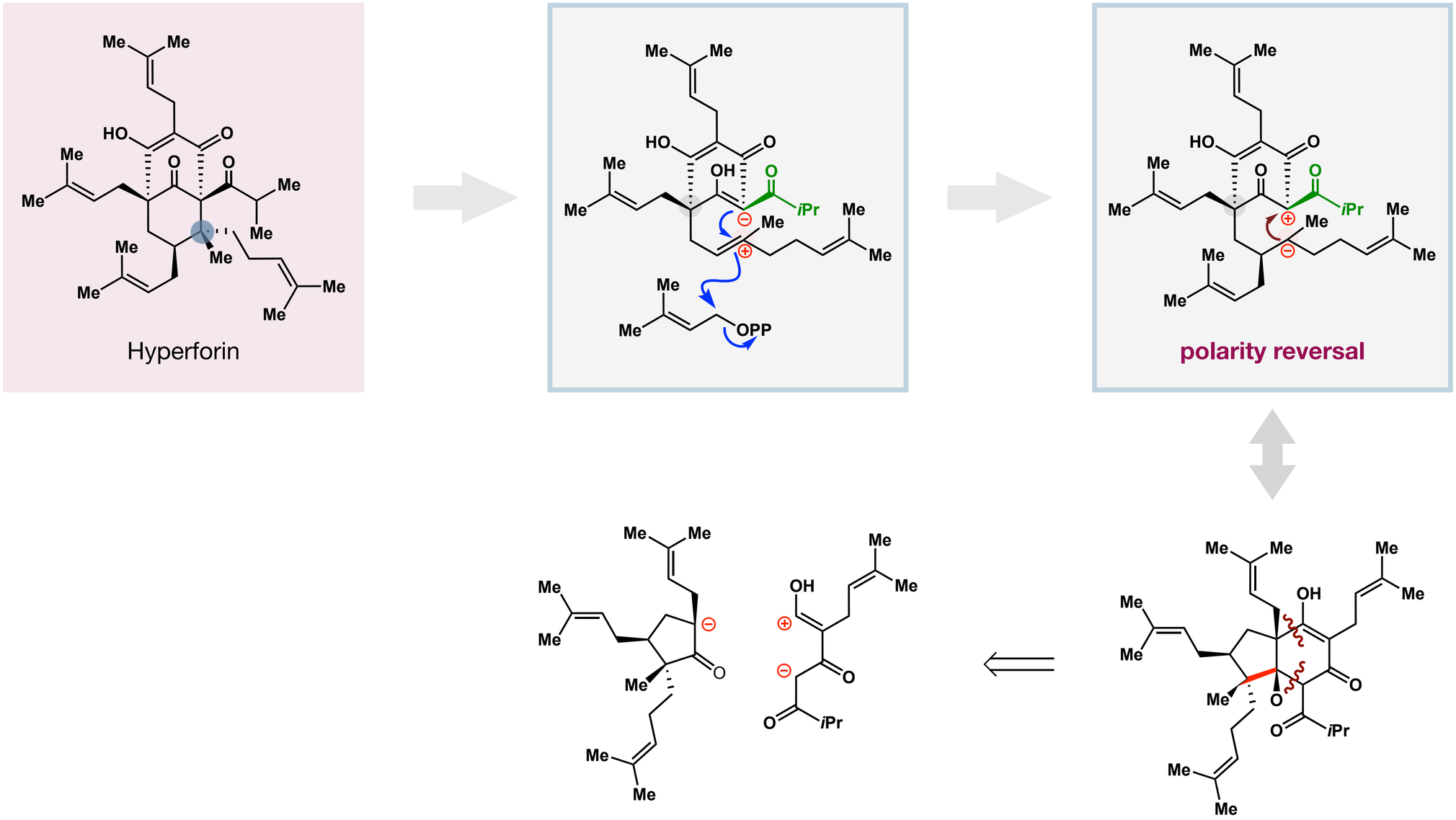

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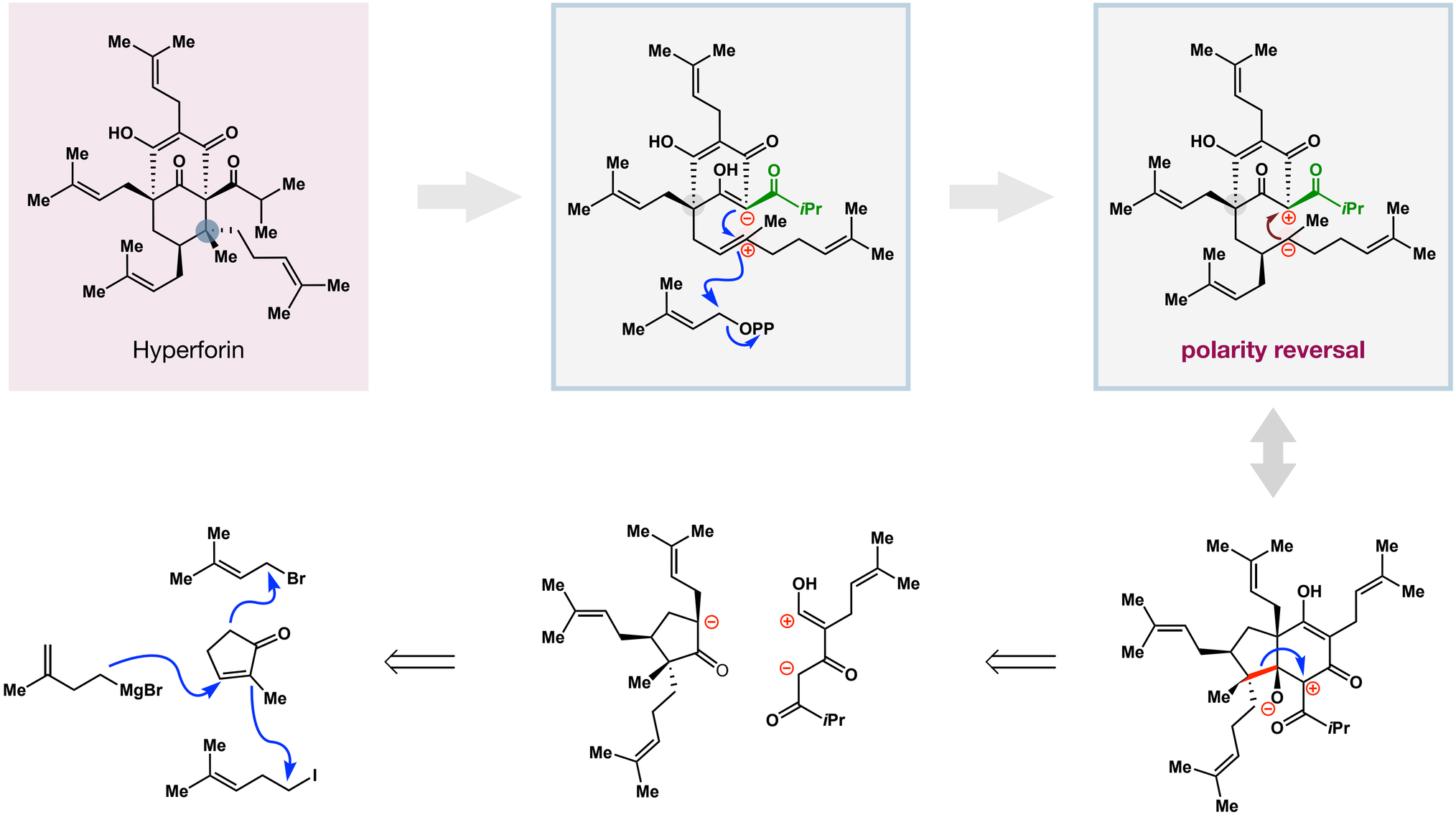

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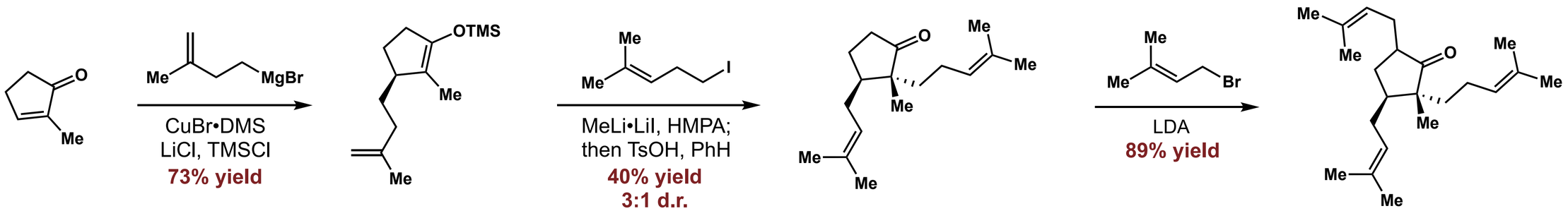

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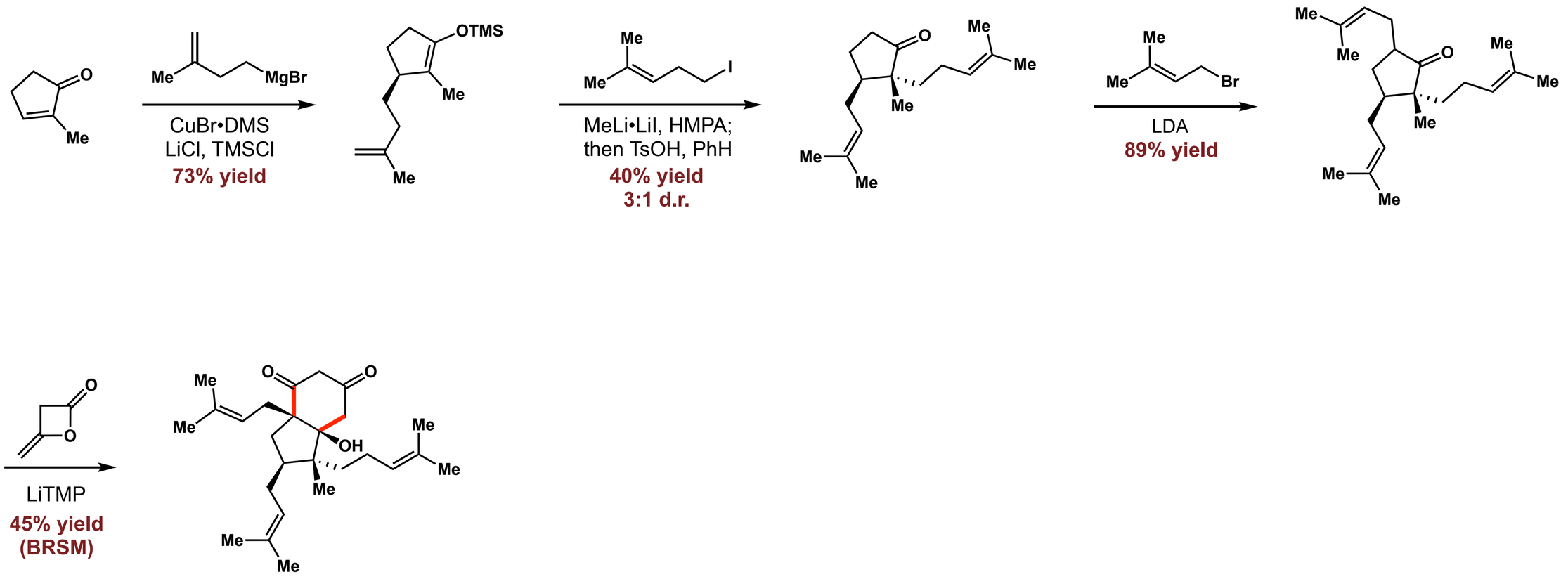

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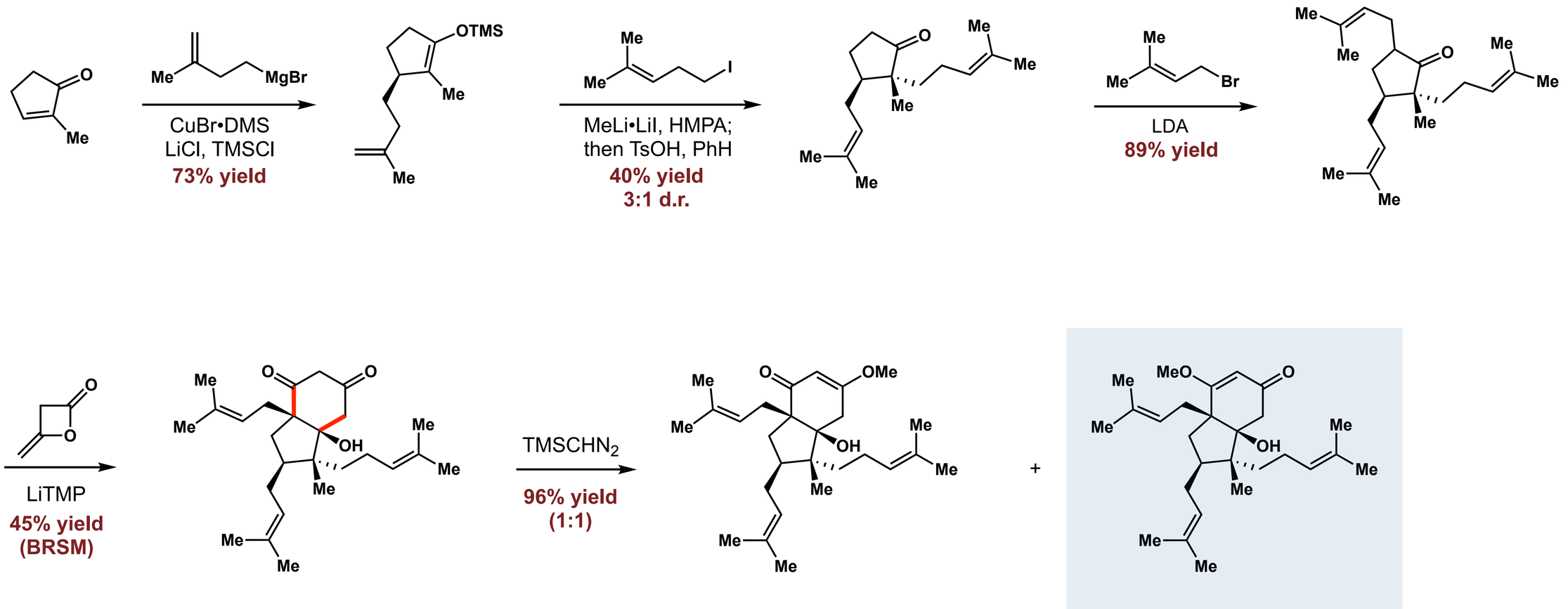

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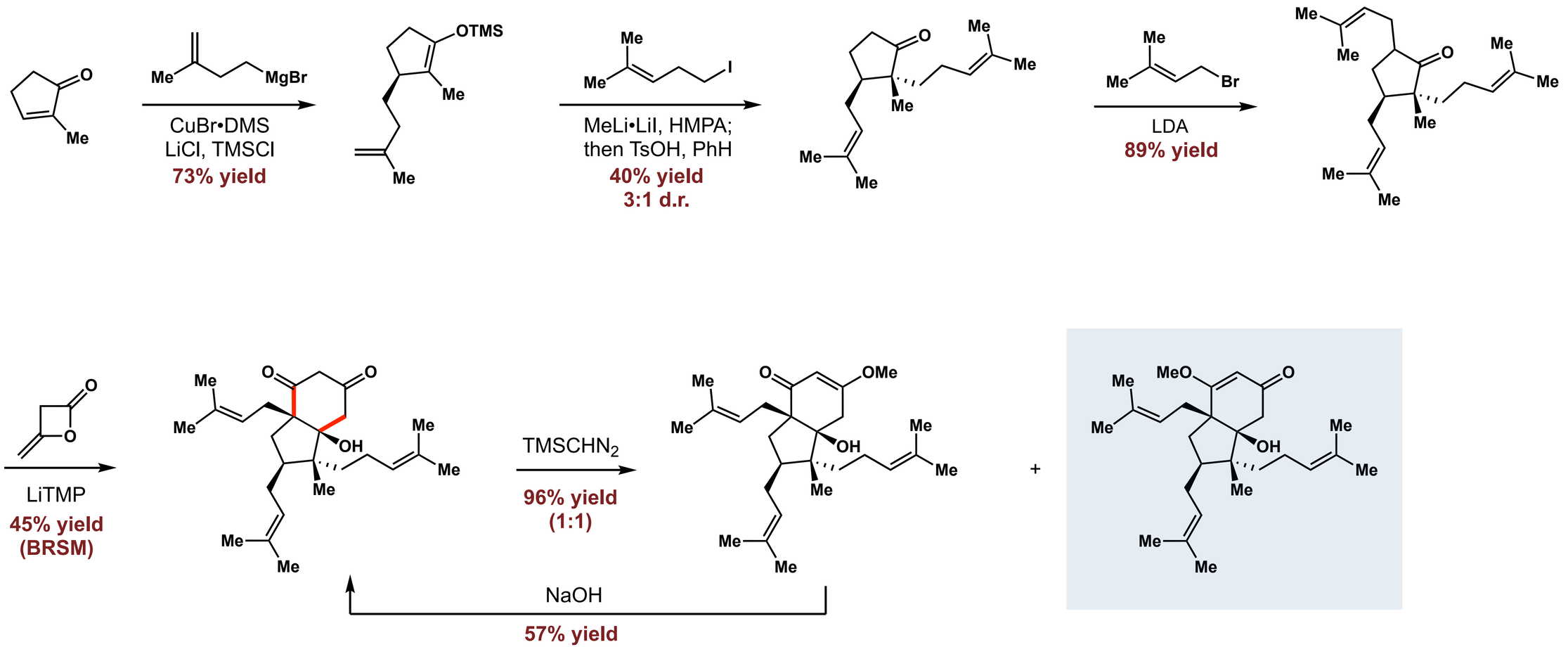

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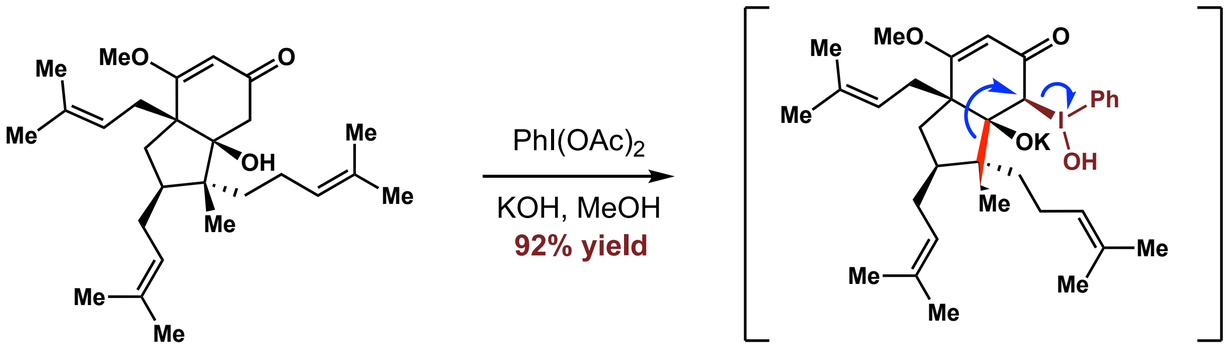

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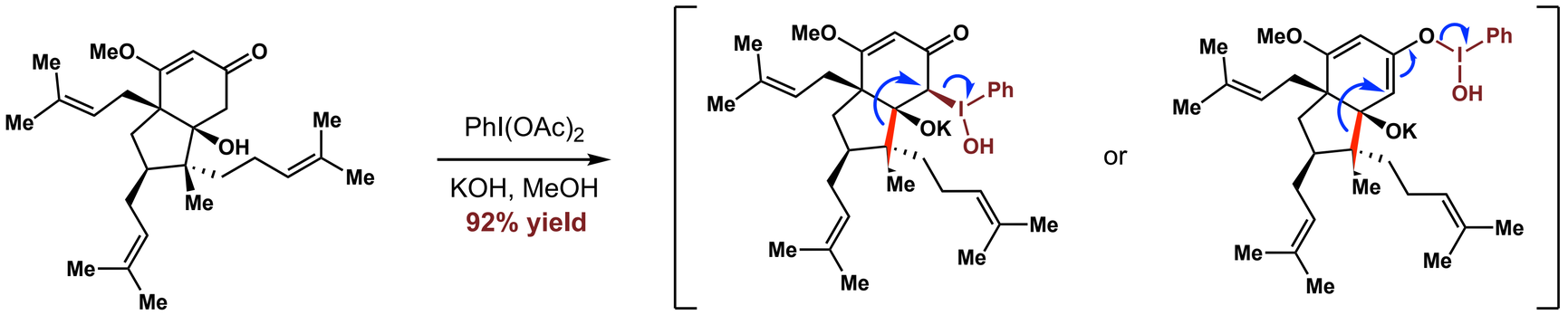

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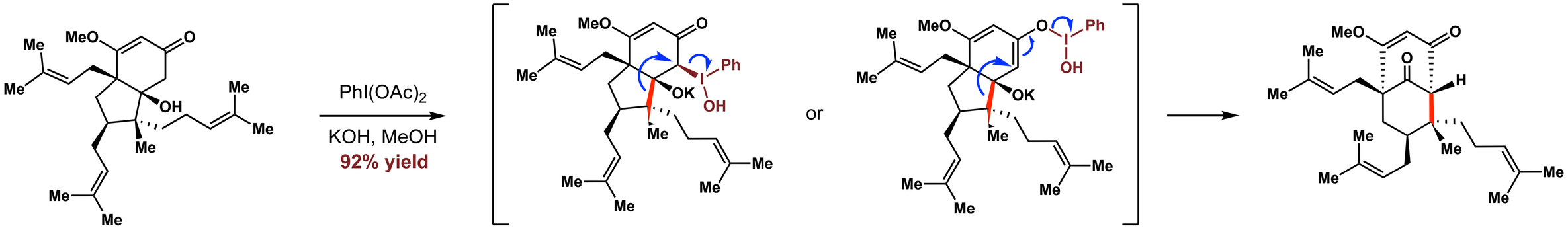

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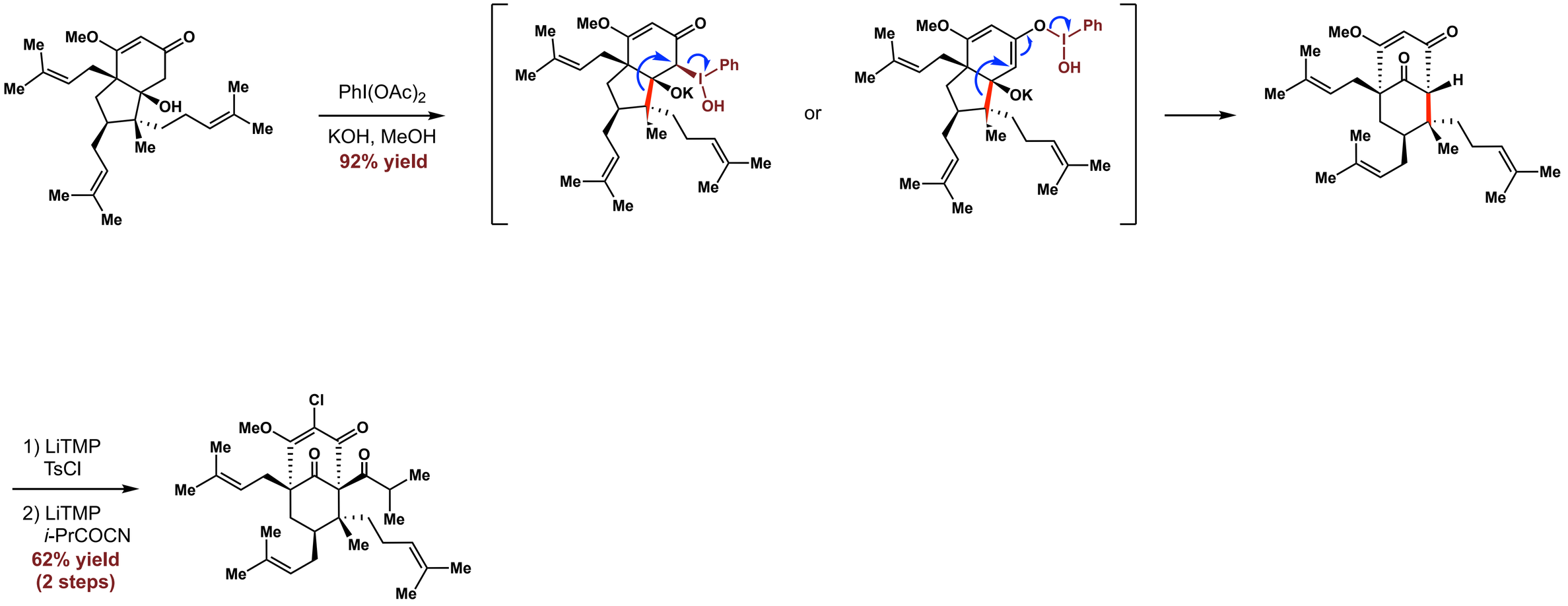

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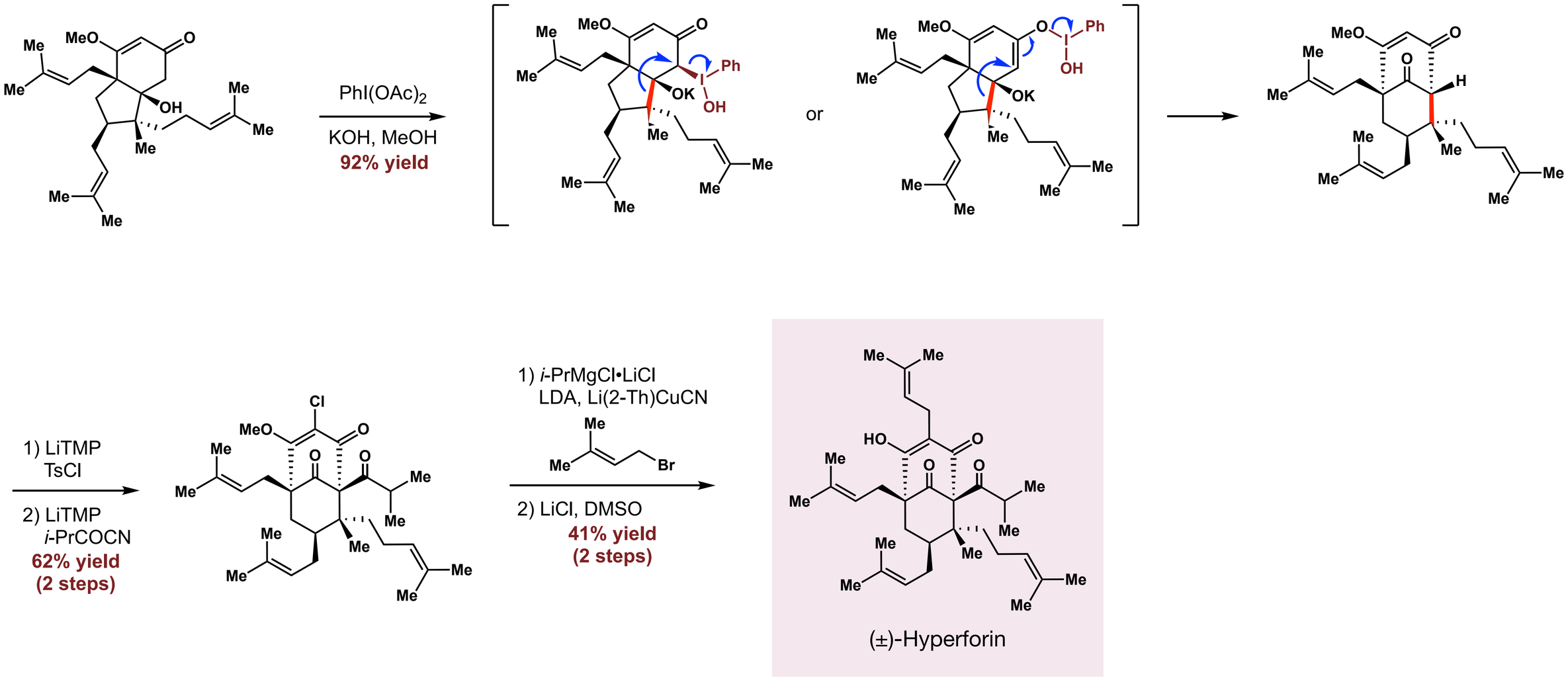

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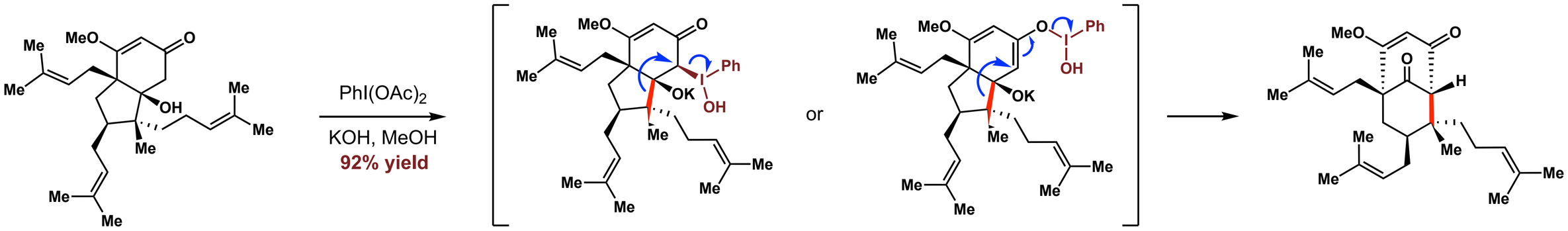

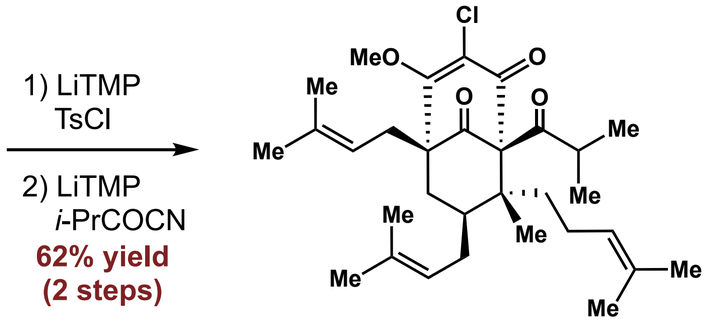

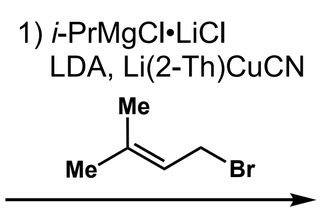

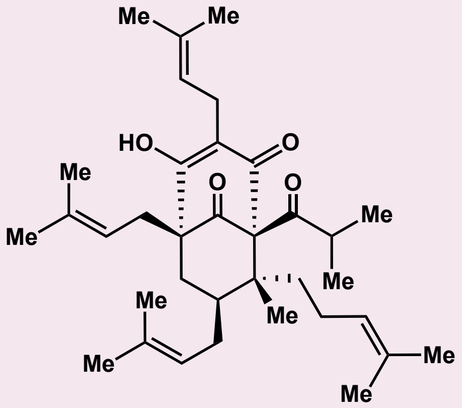

(±)-Hyperforin

Modular fragment coupling

Skeletal rearrangement

10 steps LLS

Racemic synthesis

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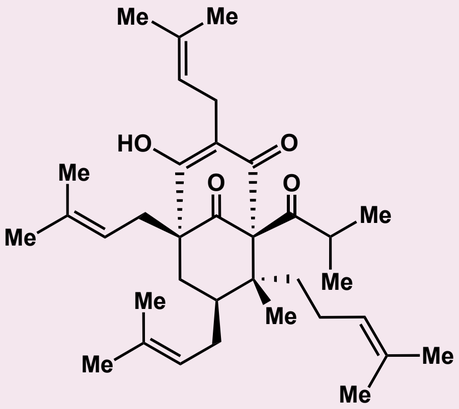

Hyperforin

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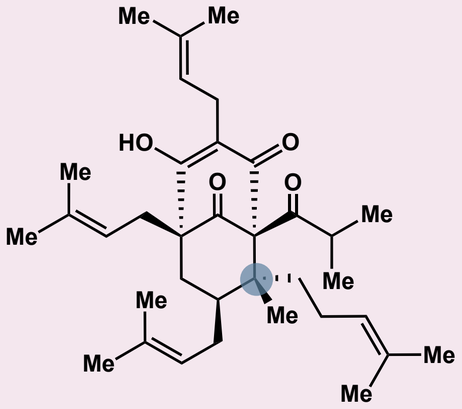
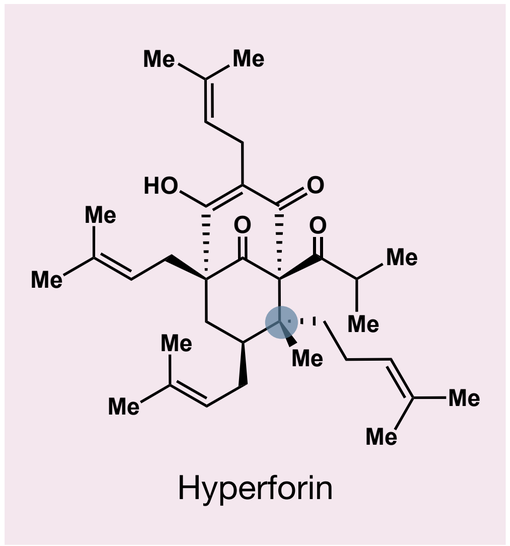
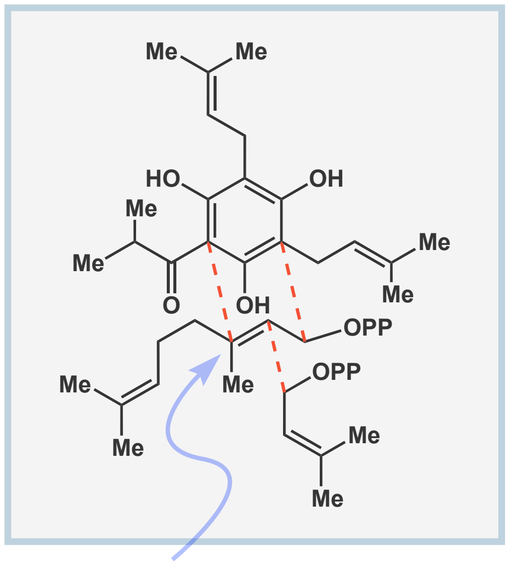
Total Synthesis of Hyperforin (Li)

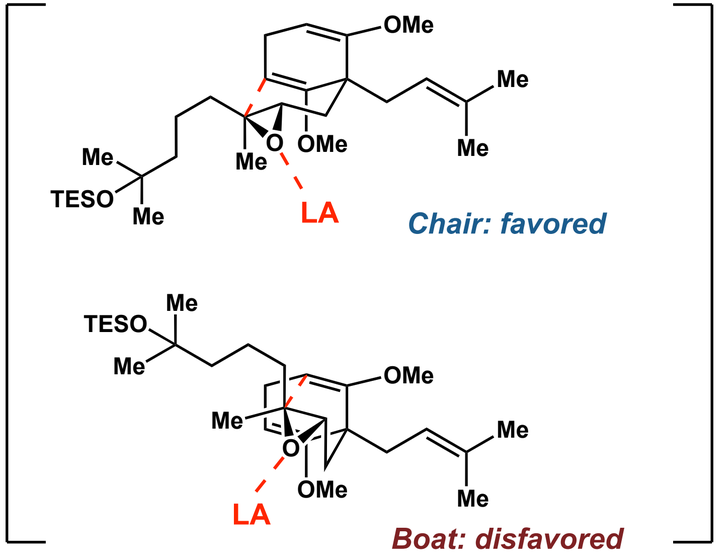


Hyperforin

Total Synthesis of Hyperforin (Li)







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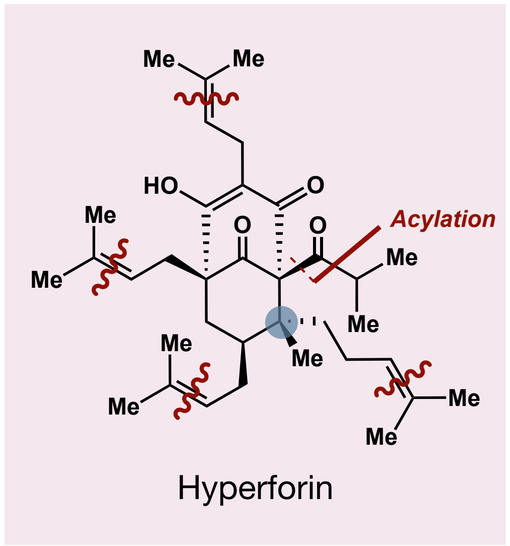

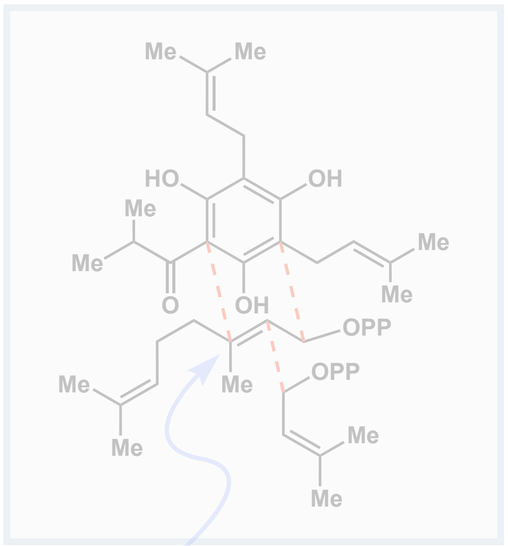

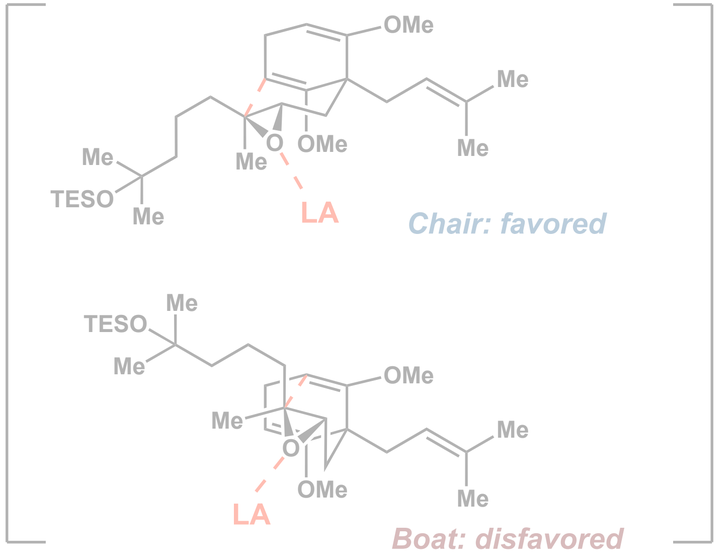

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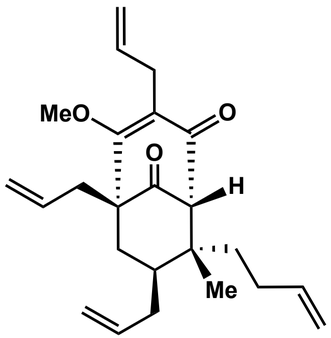
Global Cross Metathesis



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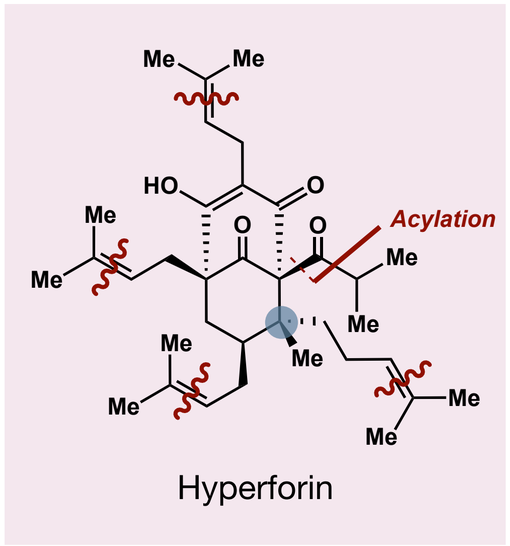
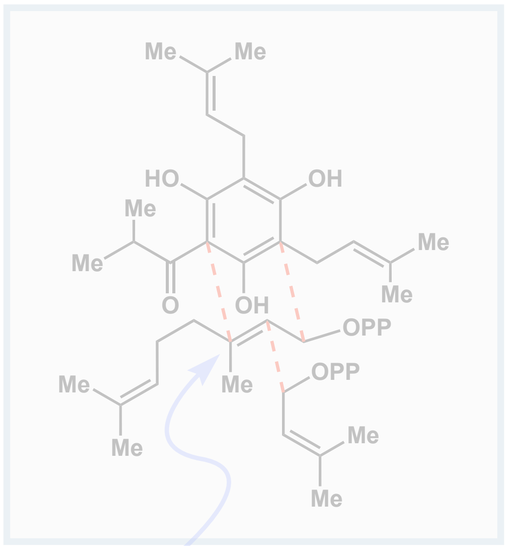
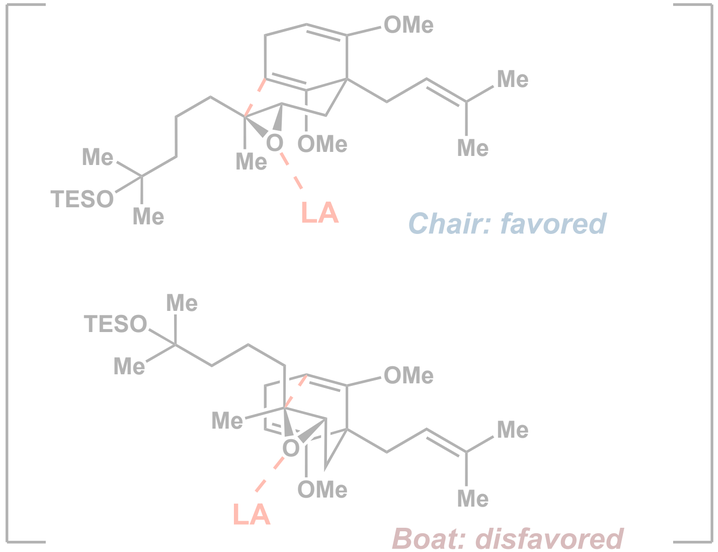
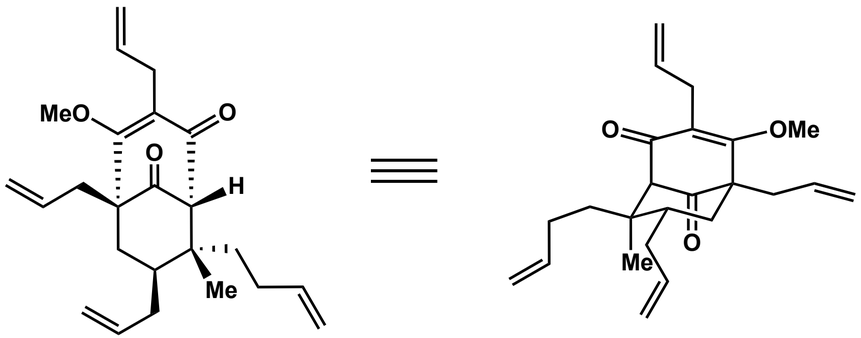






Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644.

Global Cross Metathesis



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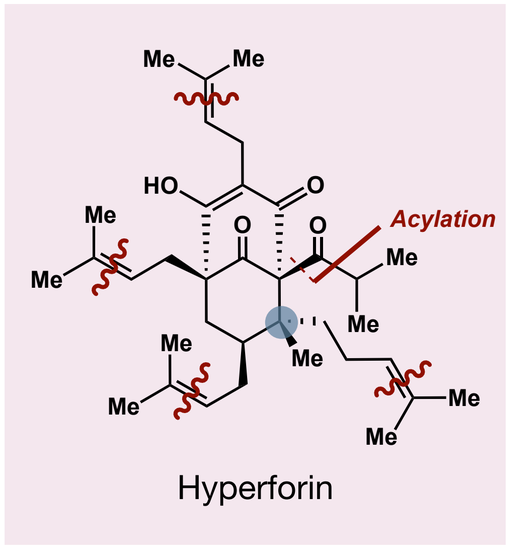

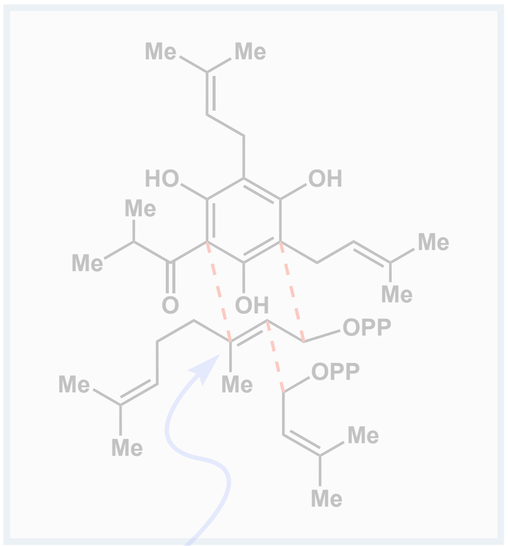

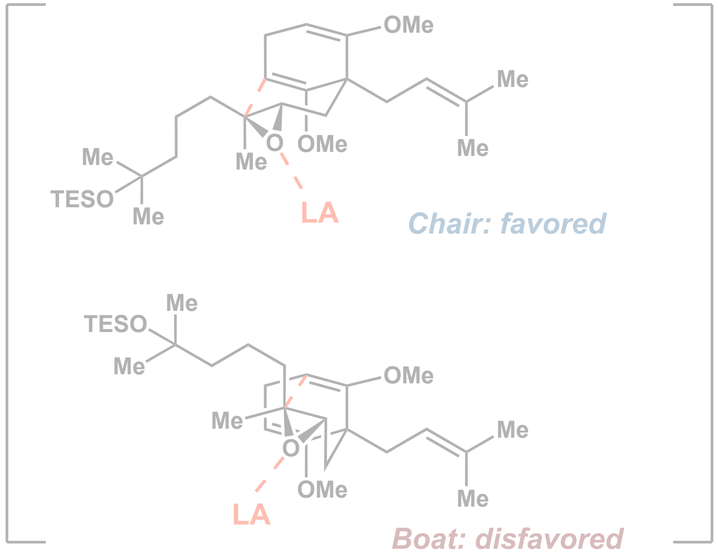

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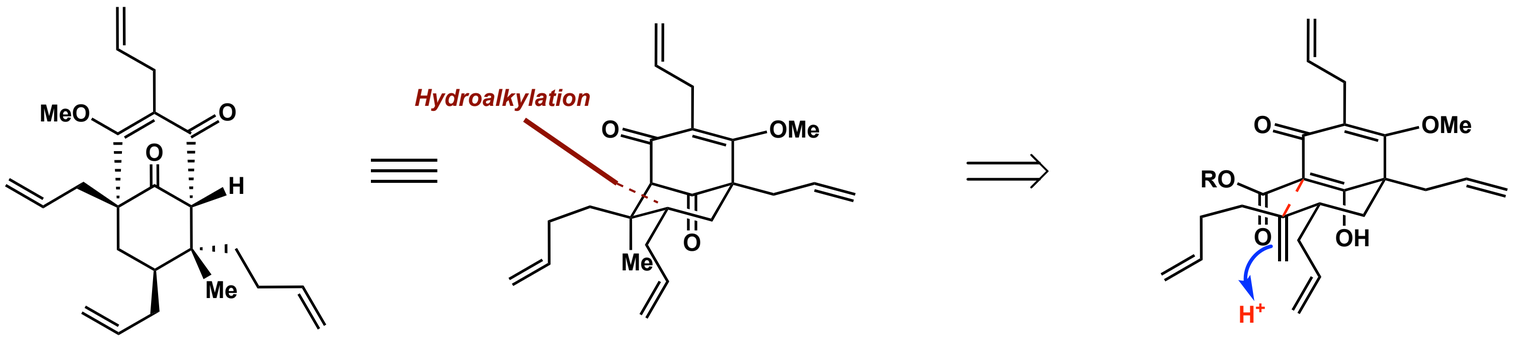

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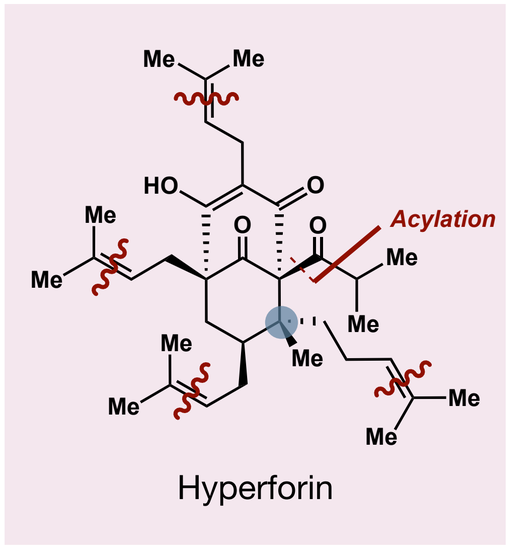

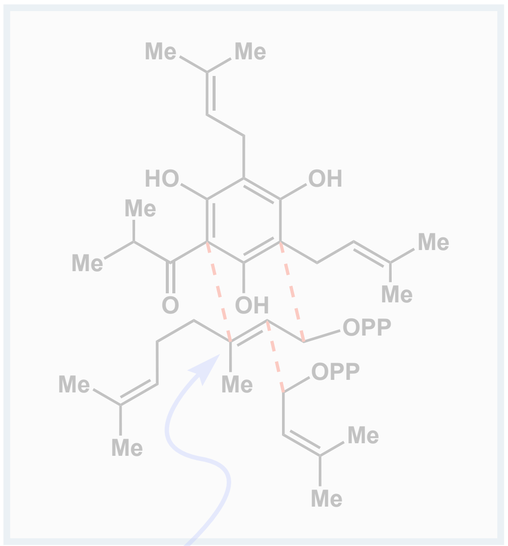

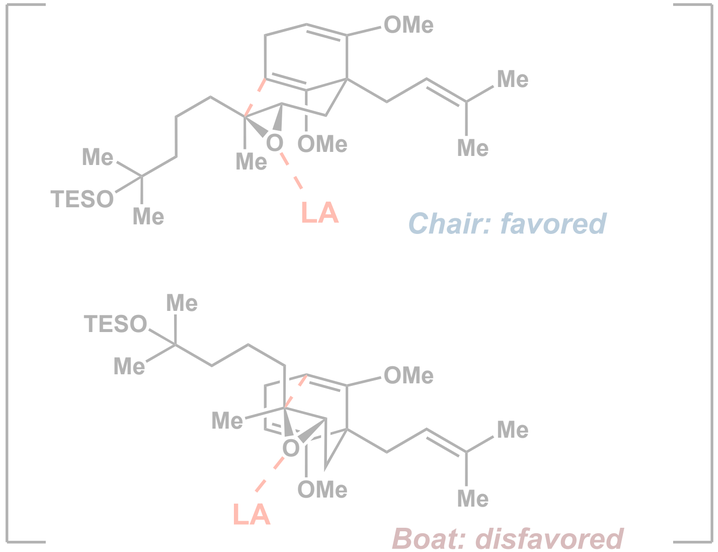

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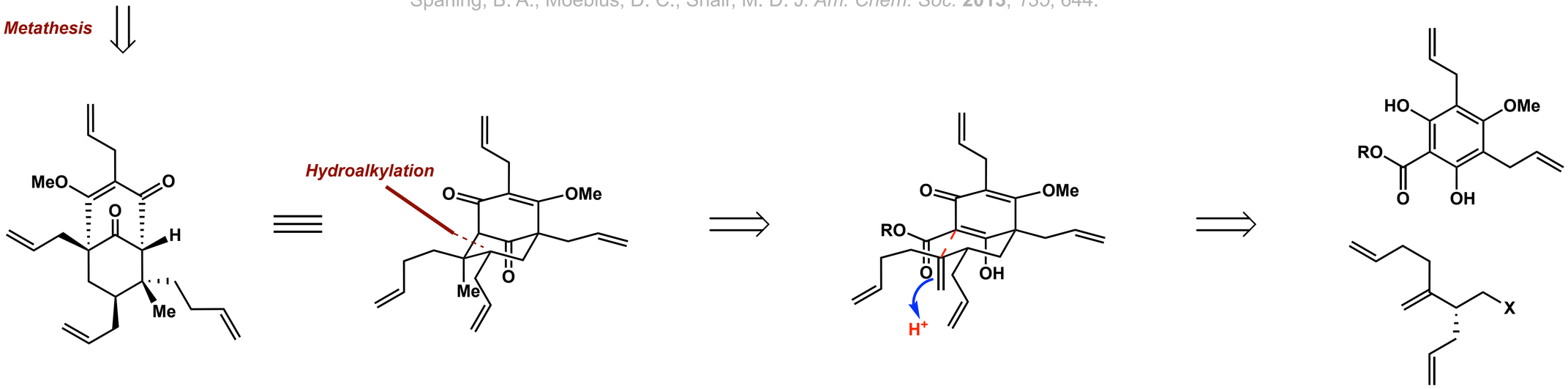

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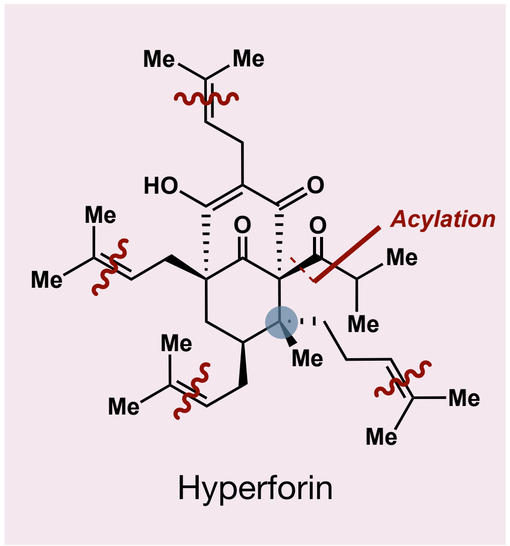

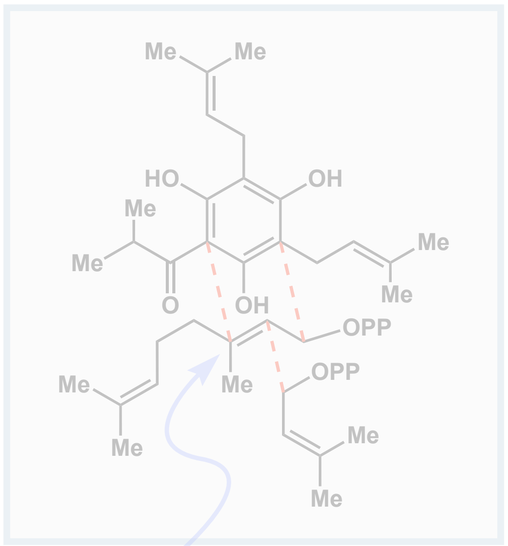

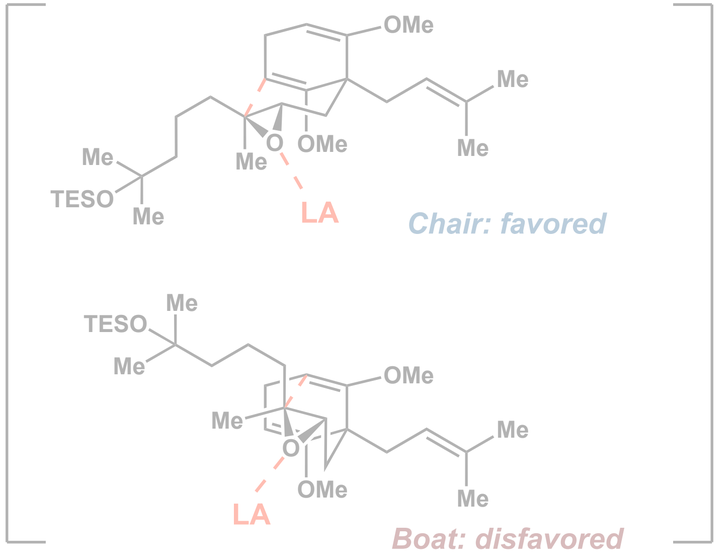

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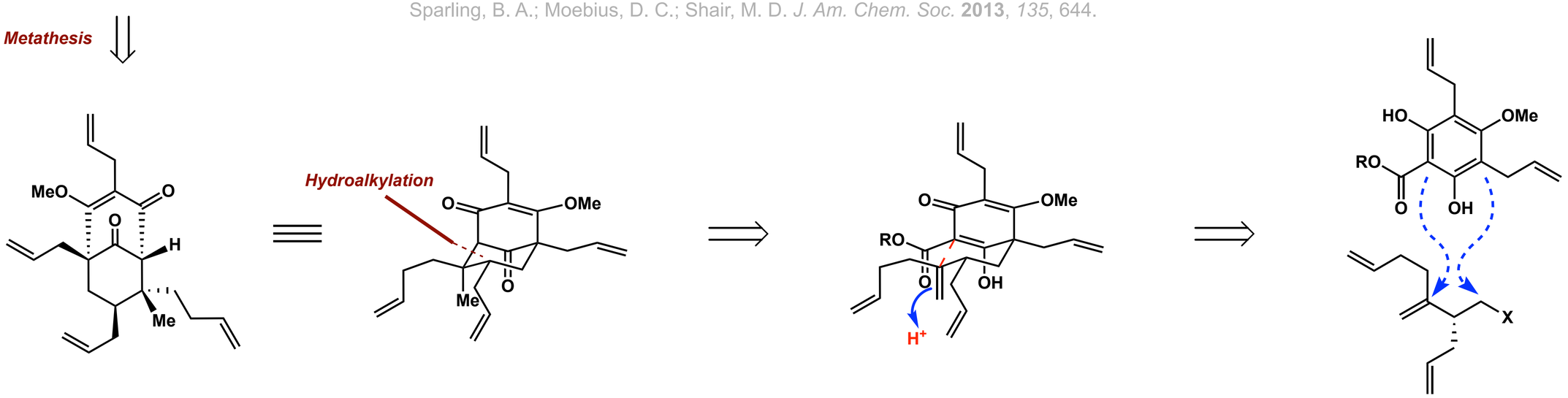

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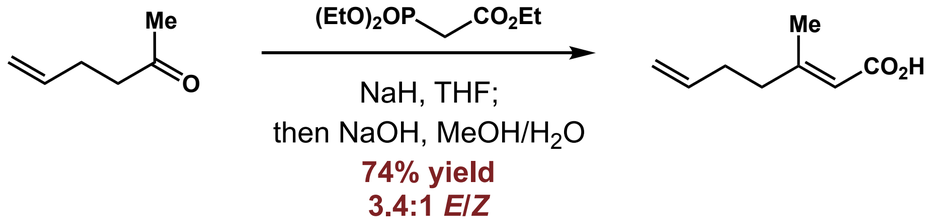

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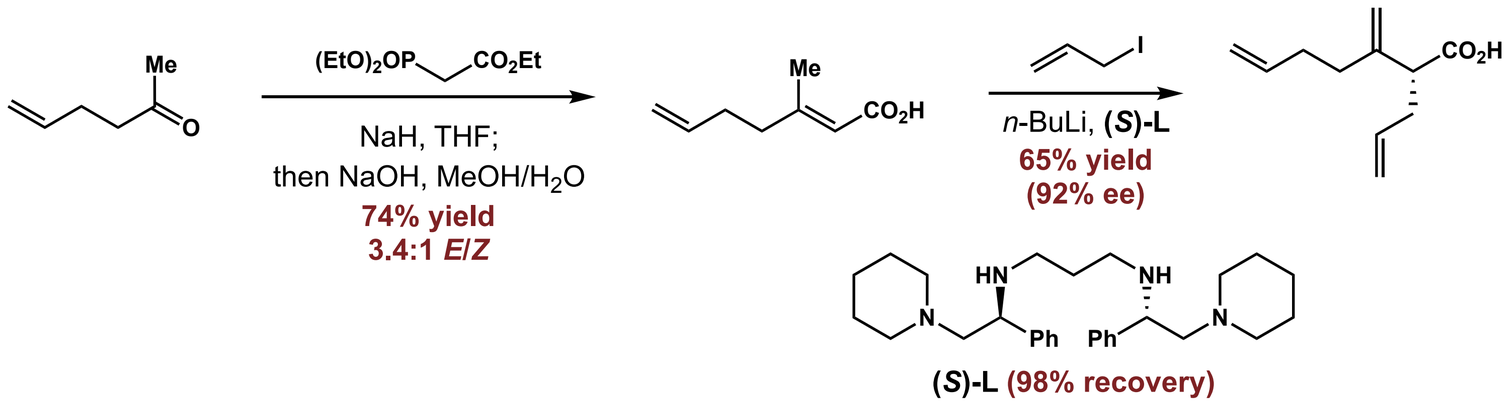

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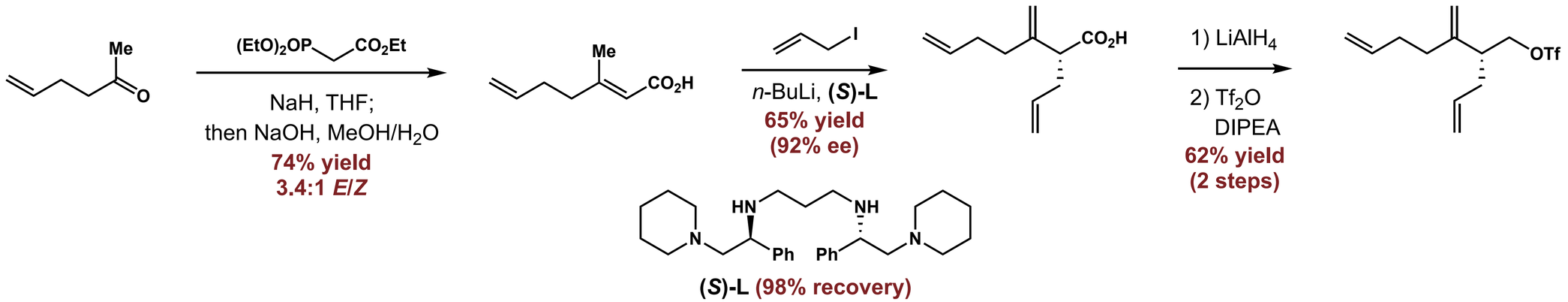

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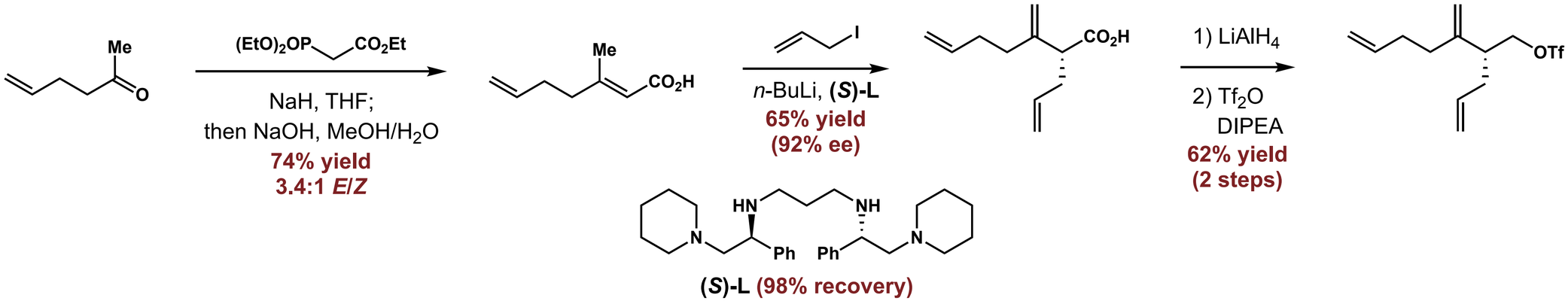

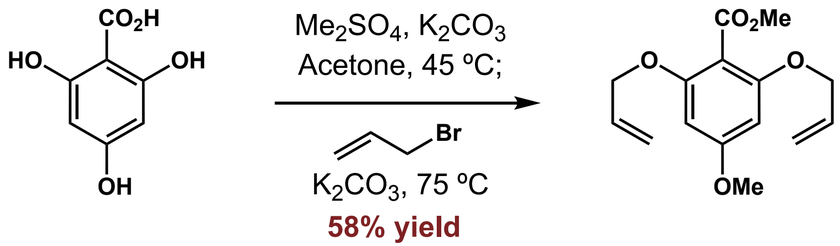

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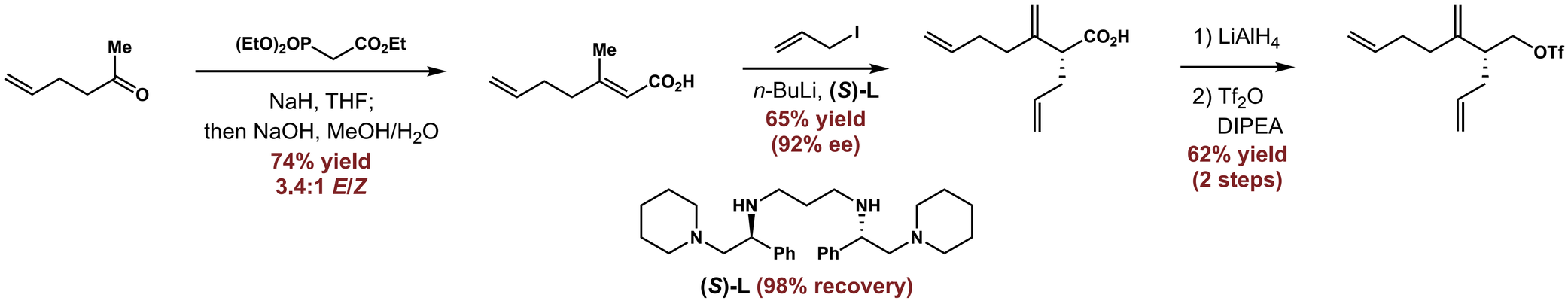

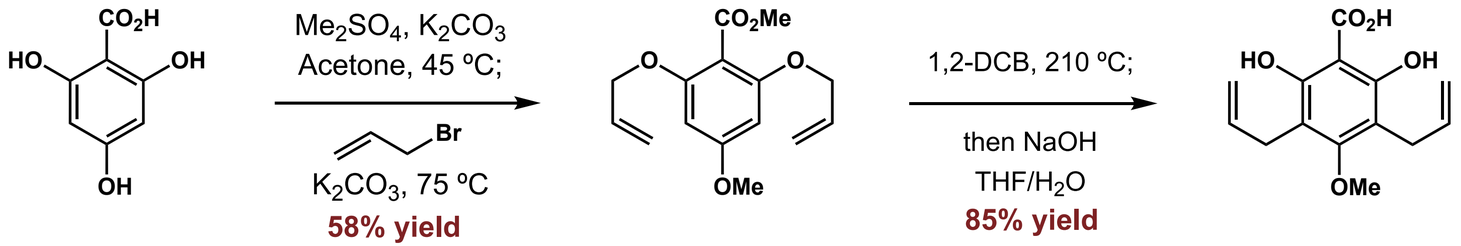

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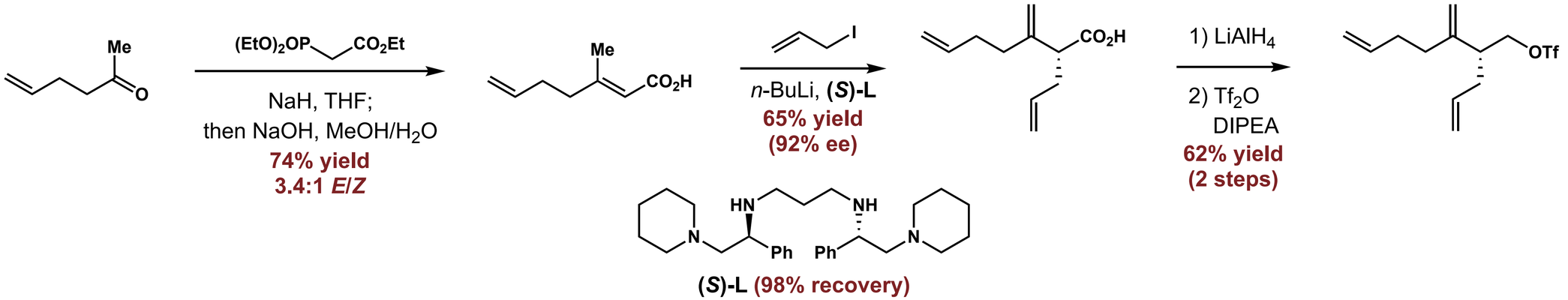

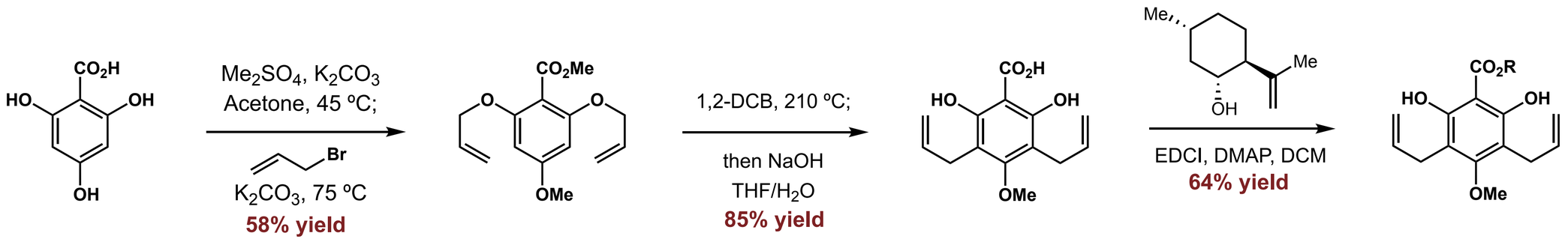

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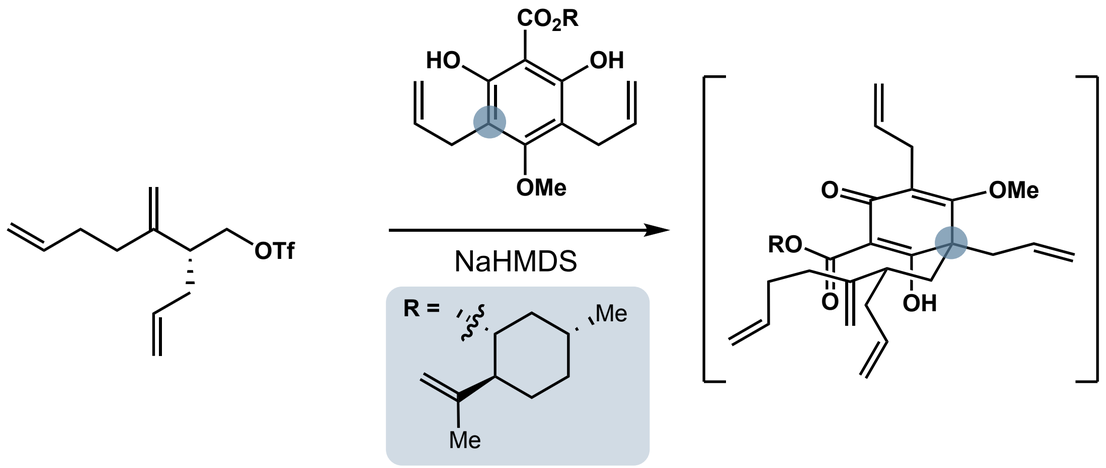

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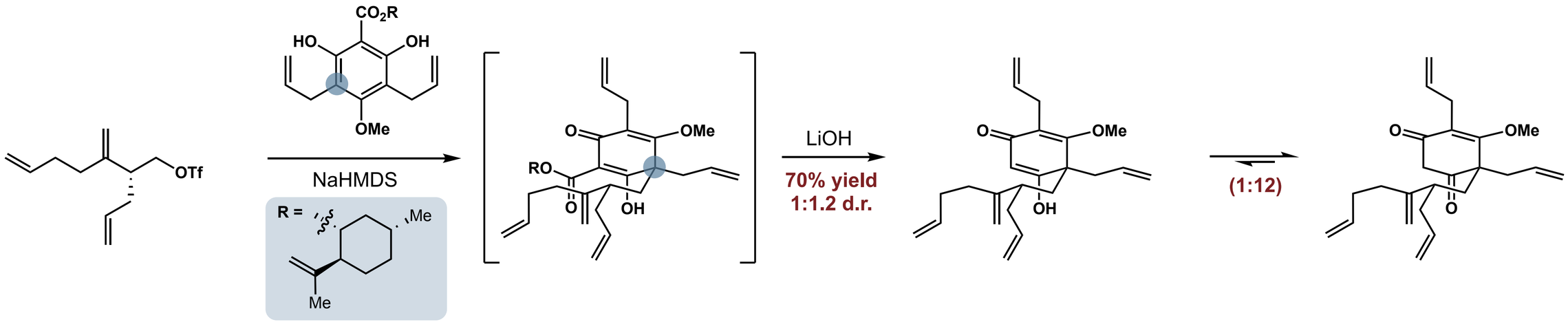

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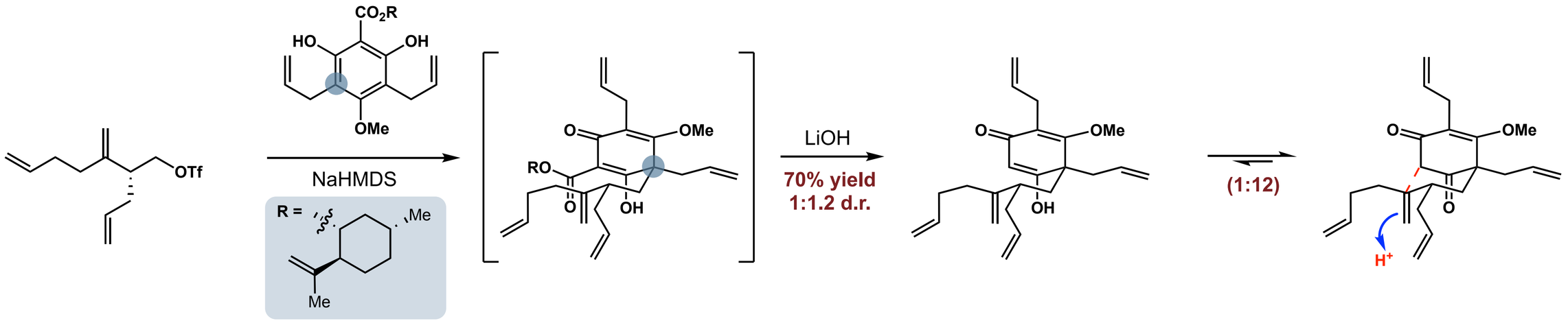

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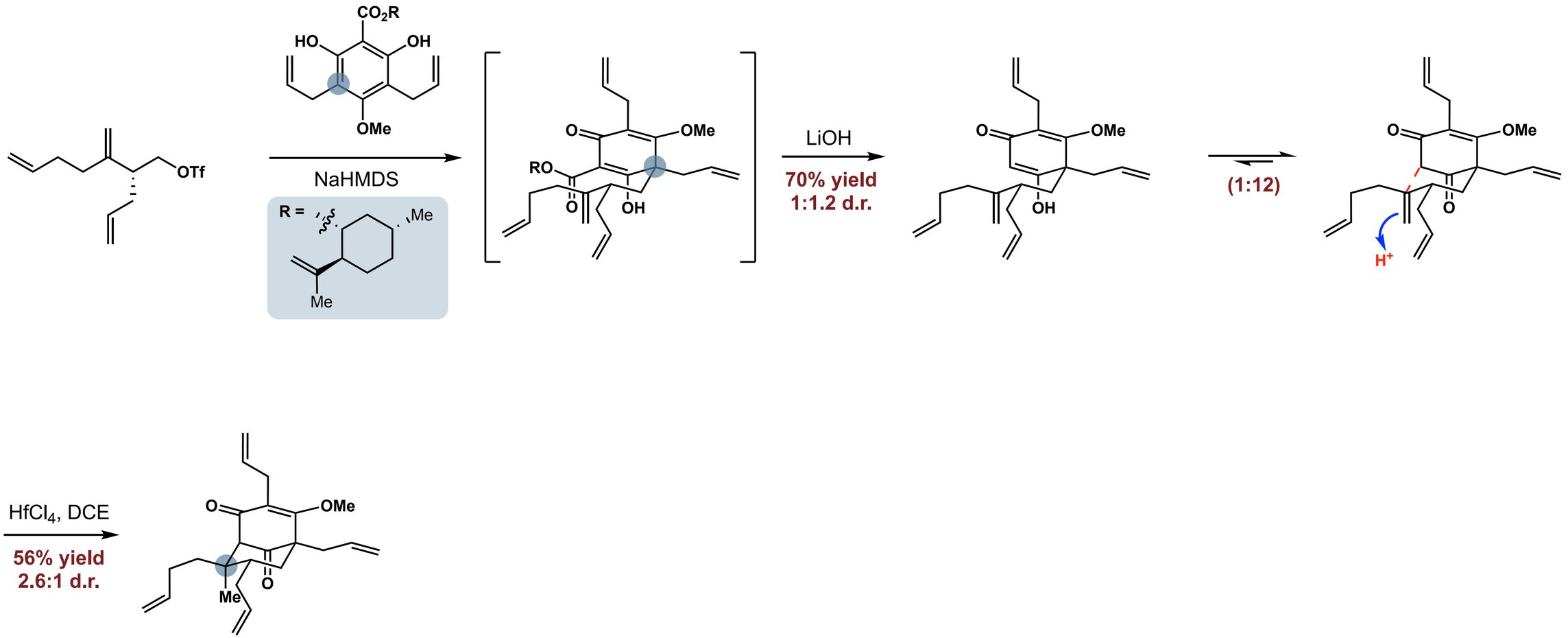

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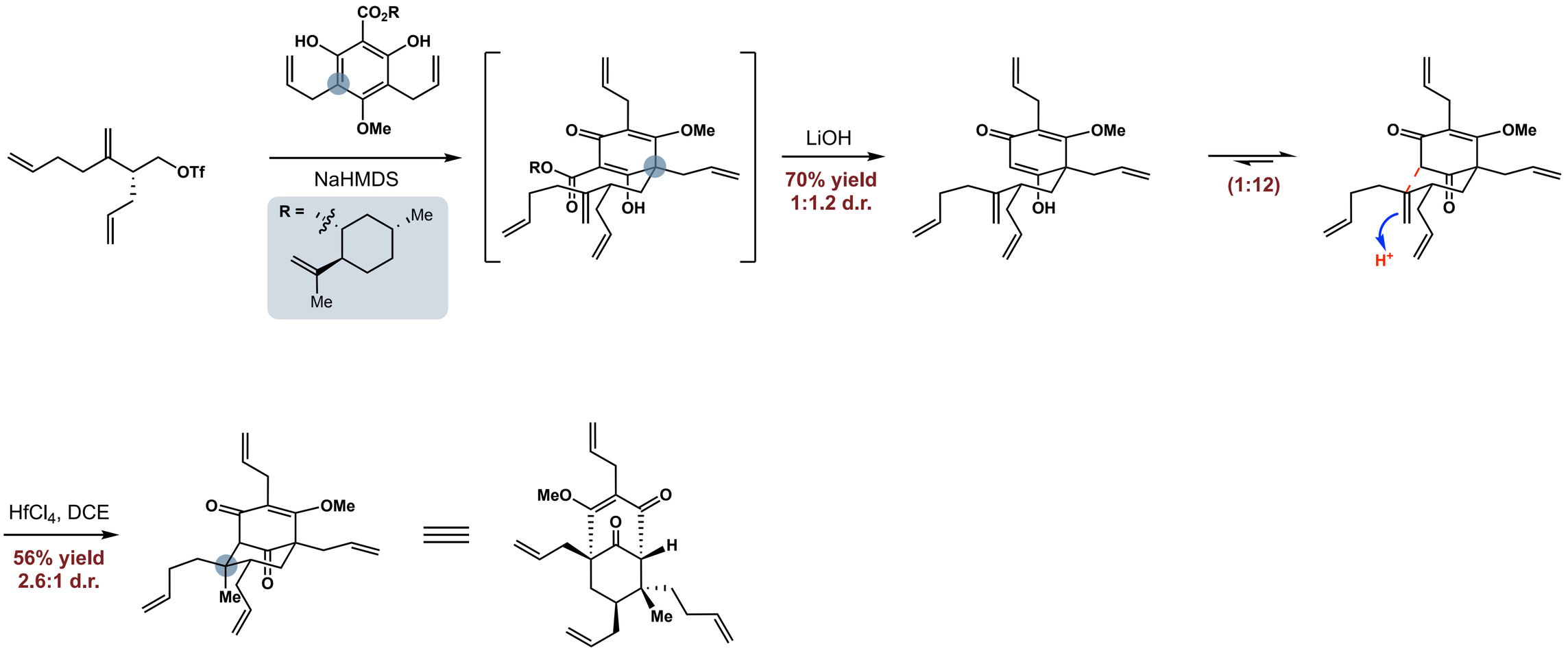

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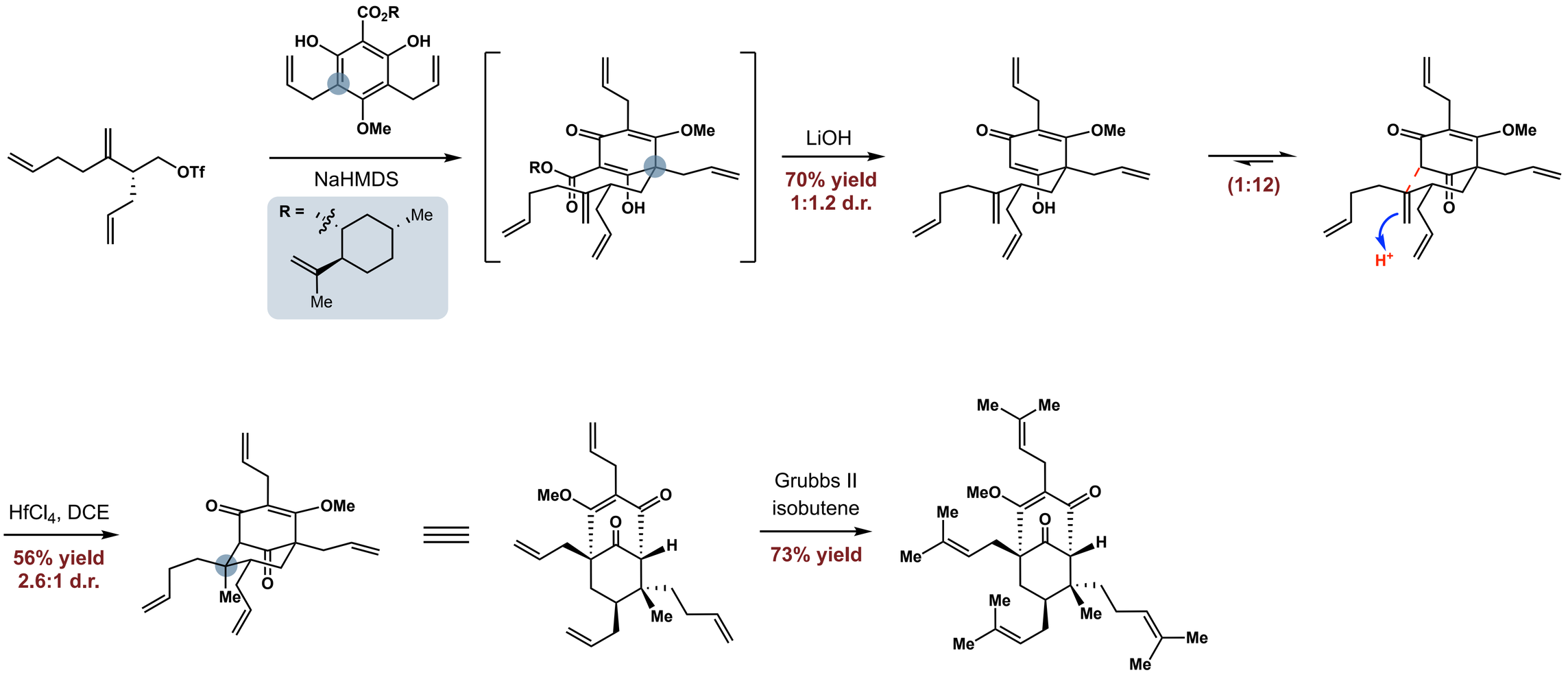

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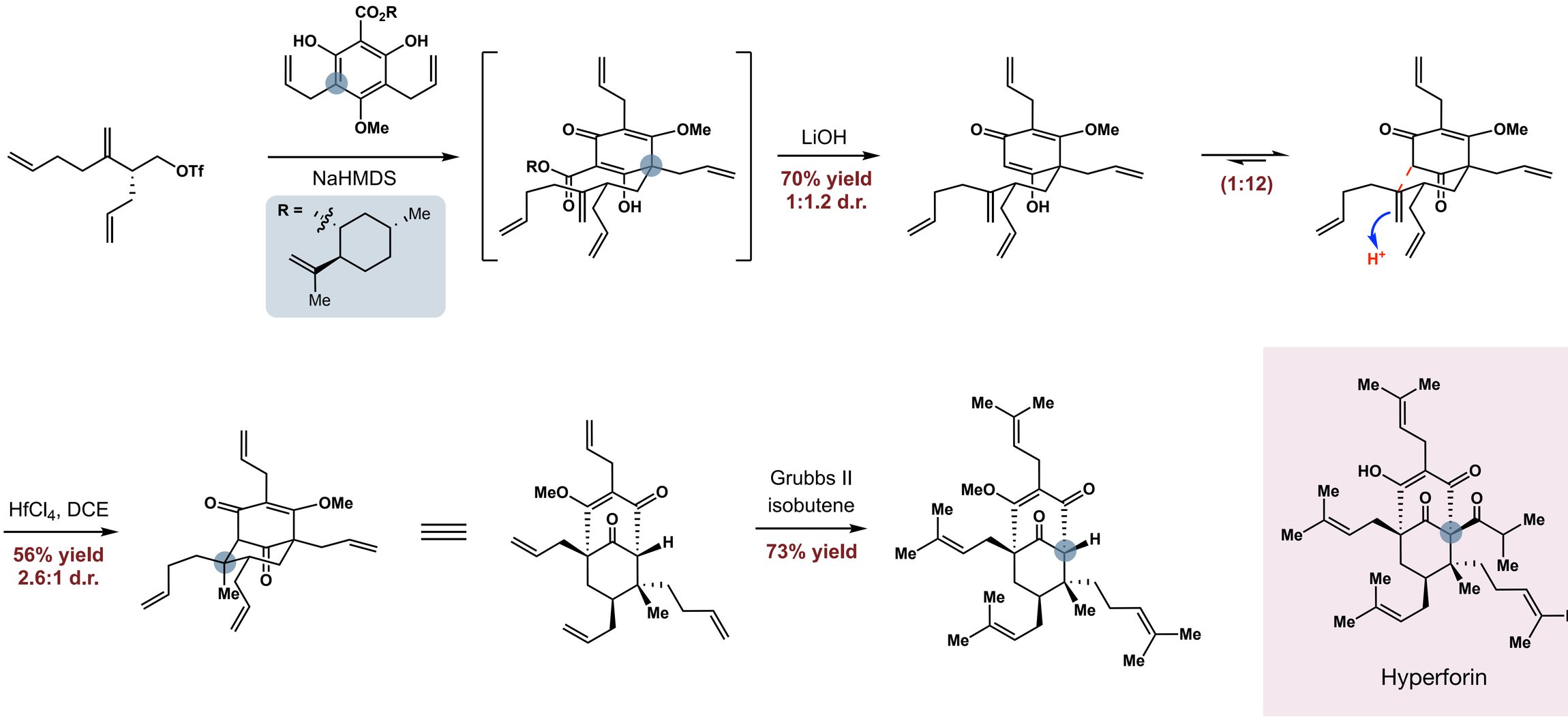

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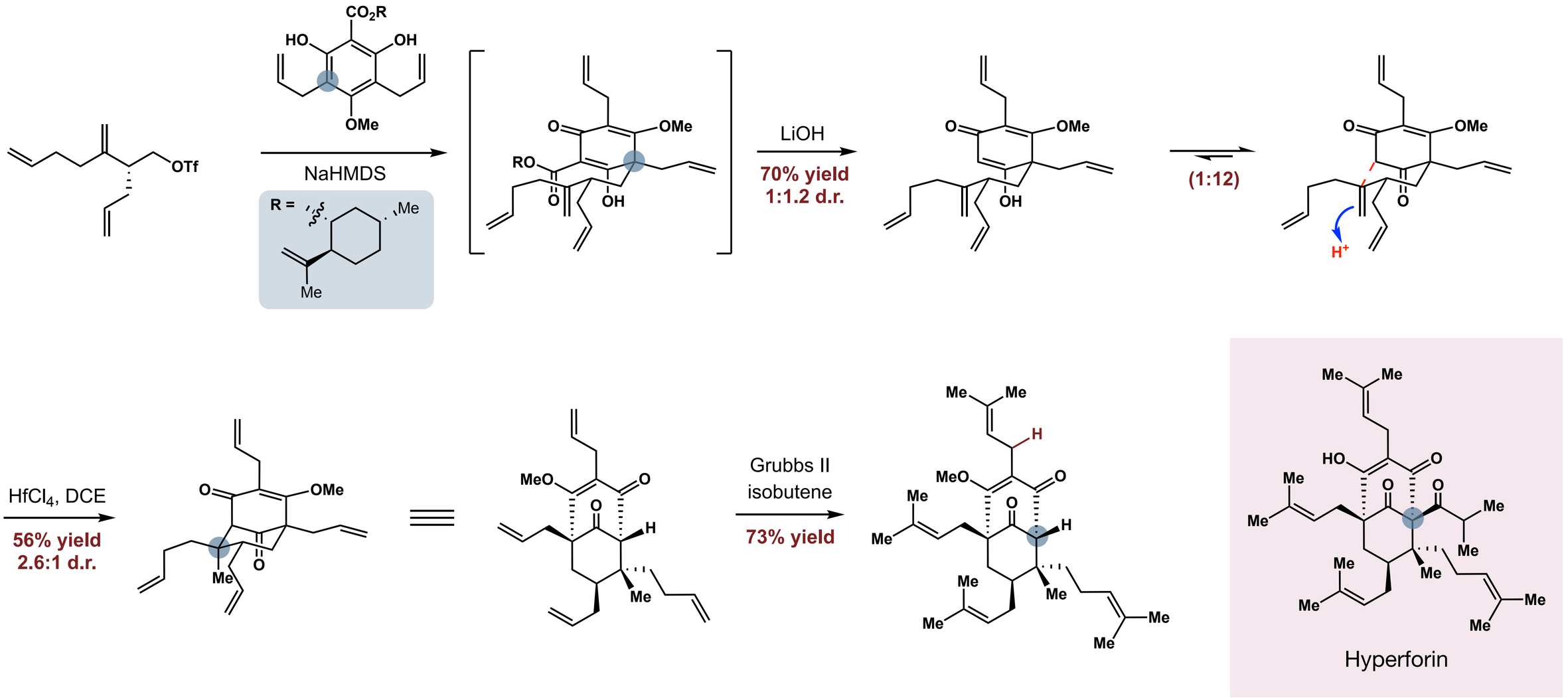

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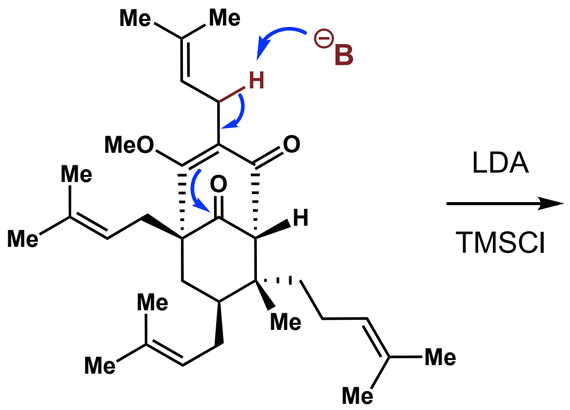
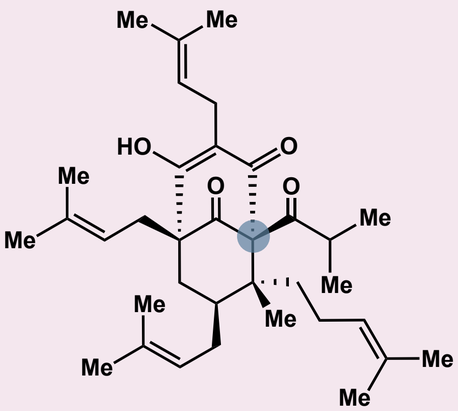


LDA

TMSCl



Hyperforin

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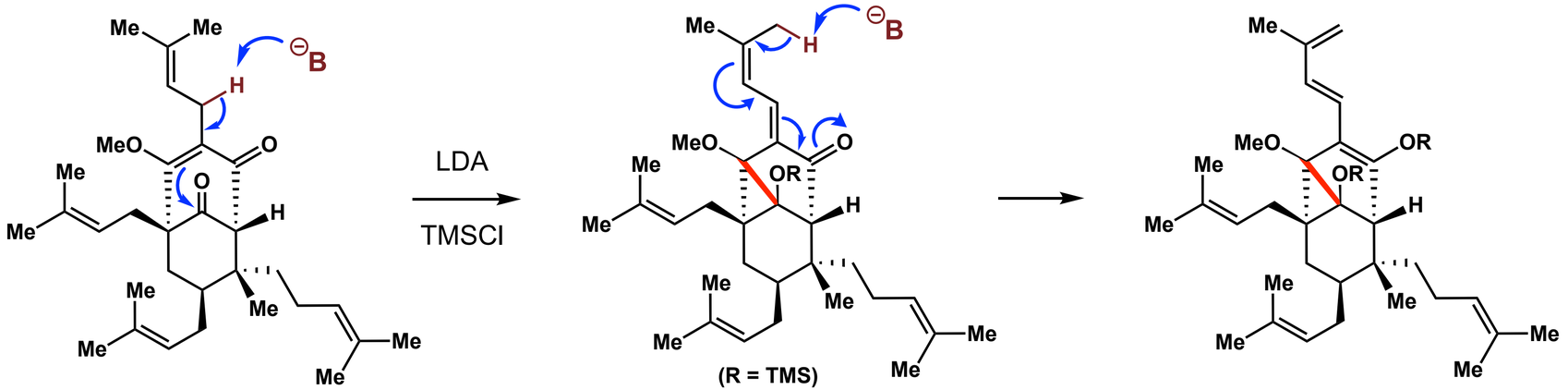

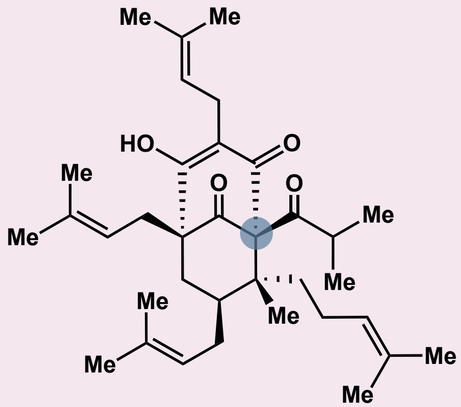

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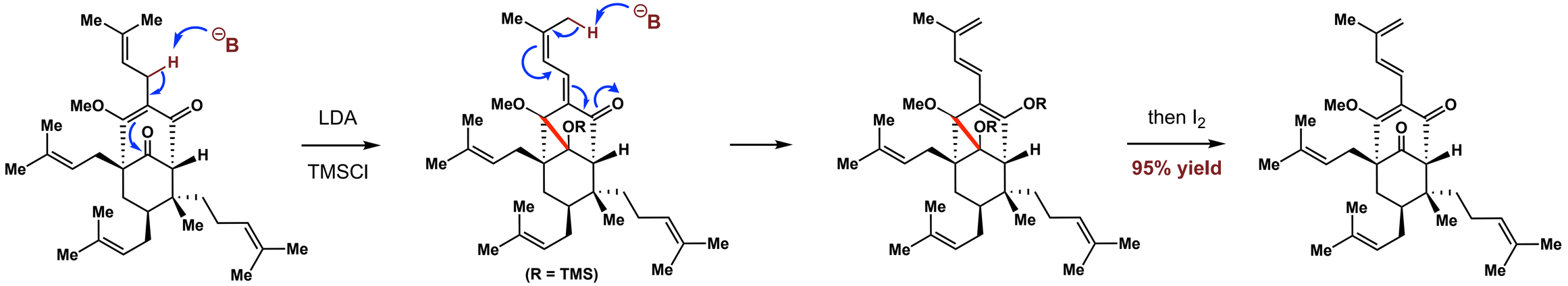

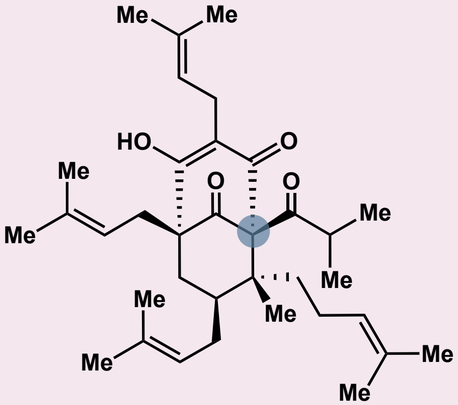

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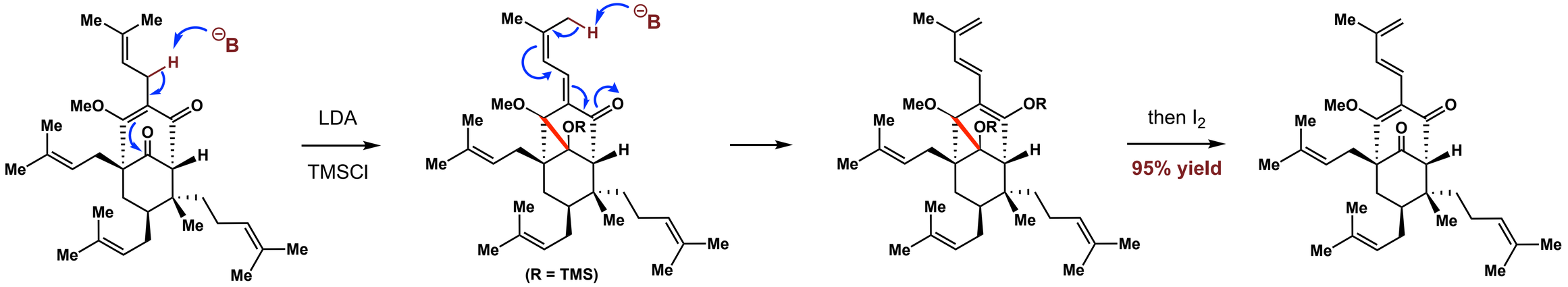

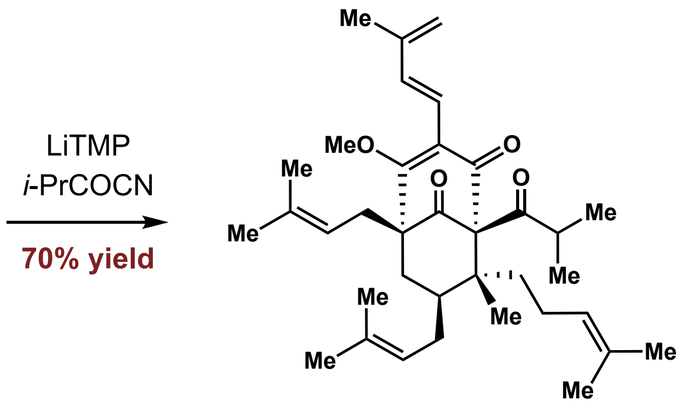

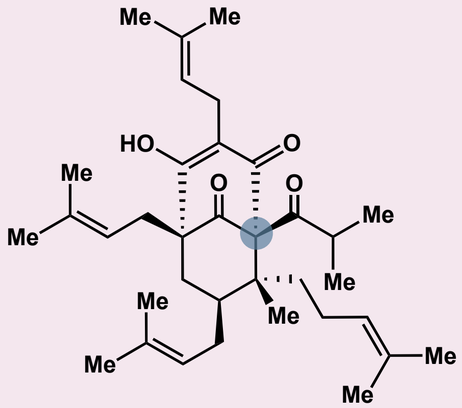

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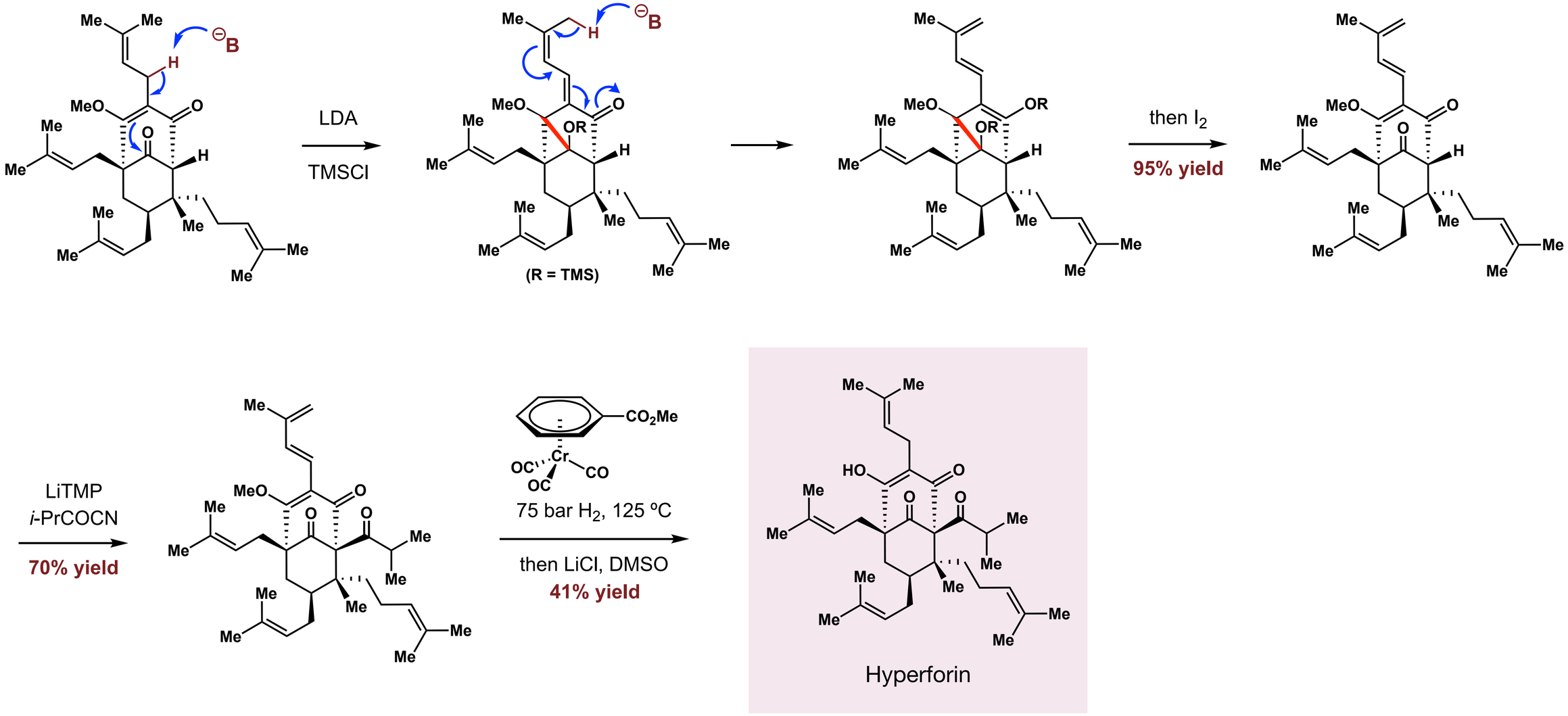

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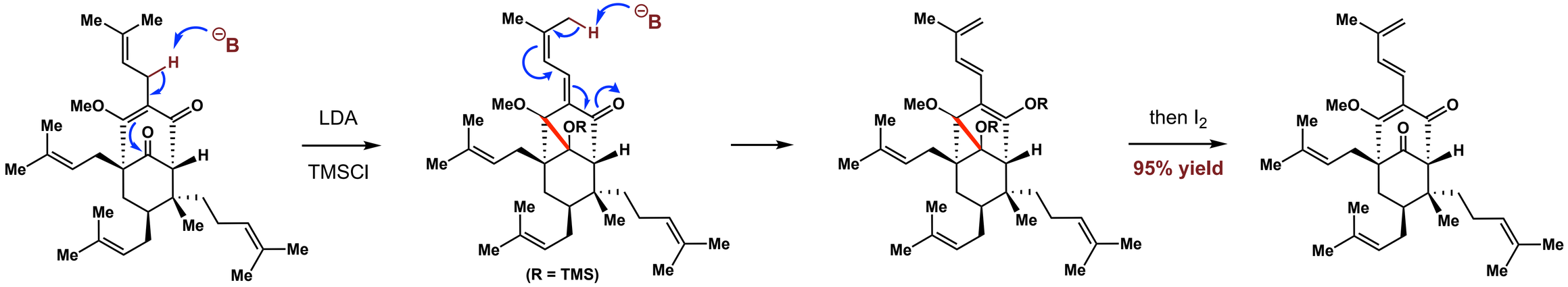

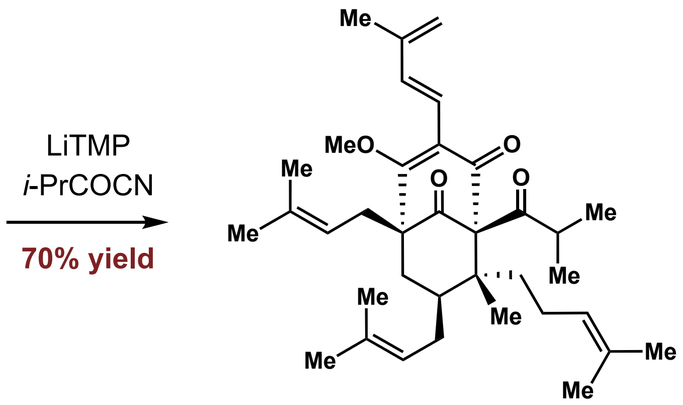

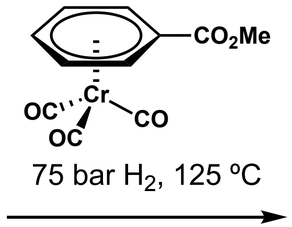

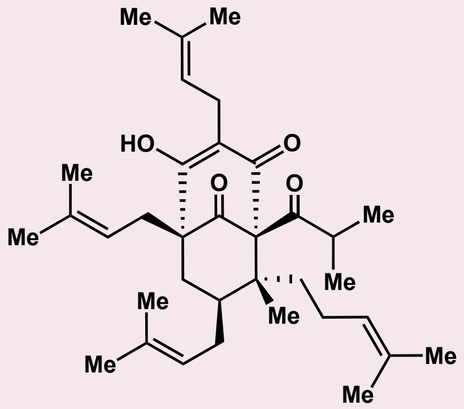

Hyperforin

Biomimetic cyclization

Convergent synthesis

Asymmetric synthesis

9 steps LLS

Poor stereoselectivity

Li, Y.; Hong, B.; Franzoni, I.; Wang, M.; Guan, W.; Jia, H.; Li, H. *Angew. Chem. Int. Ed.* **2022**, *61*, e202116136.

What is the future of natural product total synthesis?

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1975: Structure Elucidation

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2013: M. Shair (**18 steps LLS**)

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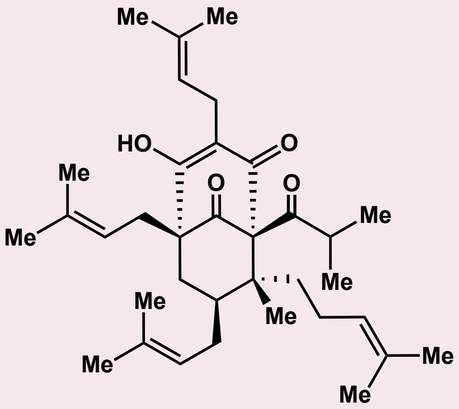

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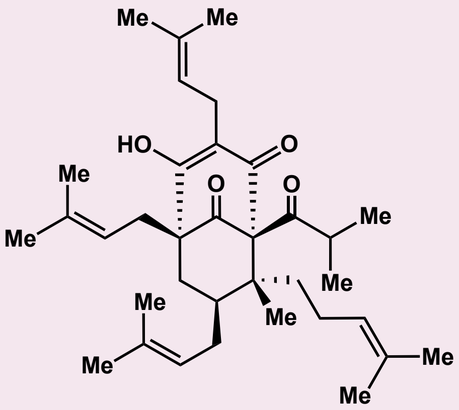
2022: H. Li (**9 steps LLS**)



Hyperforin

Biomimetic

What is the future of natural product total synthesis?

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1975: Structure Elucidation

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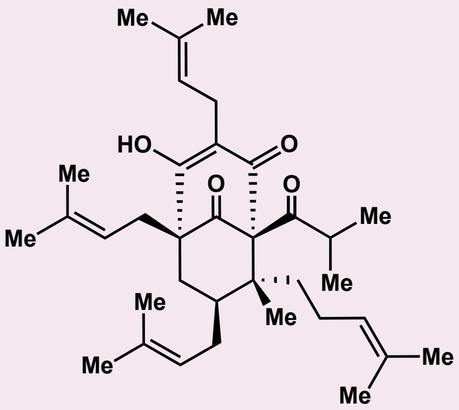

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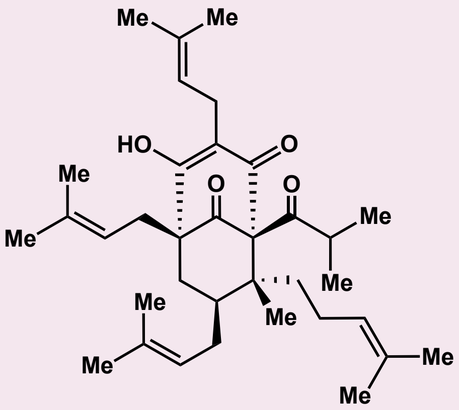

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