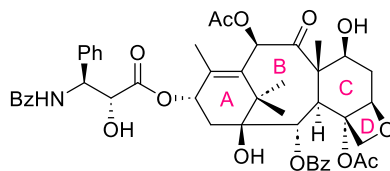


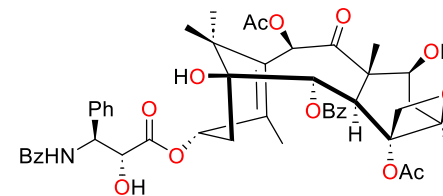
Total Synthesis of Taxol

1. Introduction
2. Synthesis Based on C9-C10
 - 2.1 Nicolaou (1994)
 - 2.2 Kuwajima (2000)
3. Synthesis Based on C10-C11
 - 3.1 Danishefsky (1995)
 - 3.2 Kishi (2000)
 - 3.3 Chida (2015 & 2022)
 - 3.4 Inoue (2023)
4. Mukaiyama (1997)
5. Baran (2020)
6. Synthesis Based on Grob Fragmentation
 - 6.1 Holton (1994)
 - 6.2 Wender (1997)
7. Li (2021)

Introduction



Taxol



Background

- isolated from the stem bark of the Pacific yew tree (*Taxus brevifolia*)
- structure fully elucidated in 1971
- most widely prescribed anticancer drug today

Structural features

- highly oxygenated [6–8–6–4] core
- 11 stereocenters, 7 contiguous chiral centers, 3 quaternary stereocenters
- extremely strained bicyclo[5.3.1]undecane ring system with an anti-Bredt bridgehead double bond between C11–C12
- highly distorted taxane skeleton in an inverted bowl shape

Relevant Reviews

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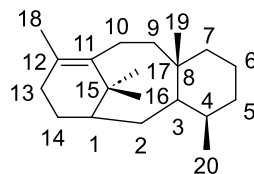
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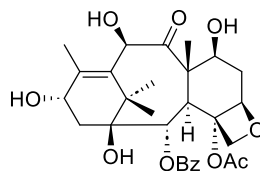
Hu, Y.-J., et al. *J. Am. Chem. Soc.* **2021**, 143,

42, 17862–17870.

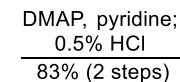
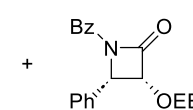
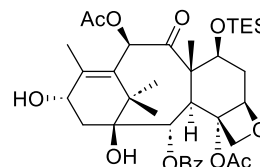
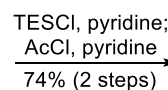
<https://doi.org/10.1021/jacs.1c09637>



taxane skeleton numbering

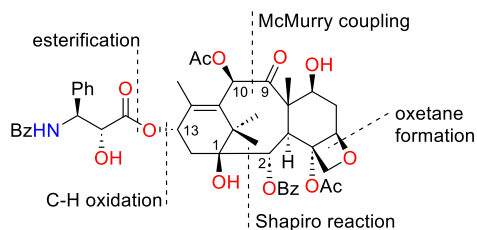


10-deacetylbaccatin III

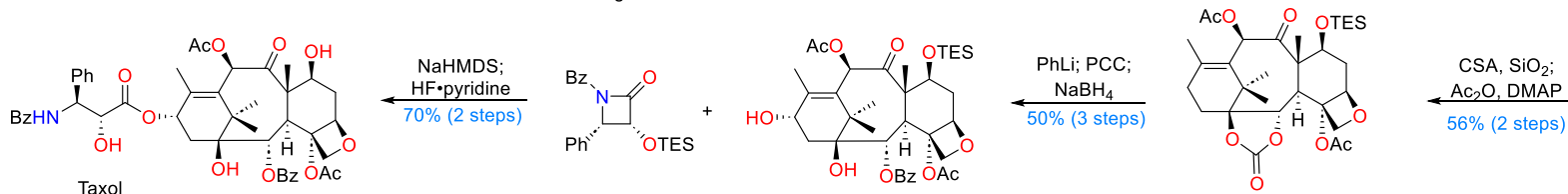
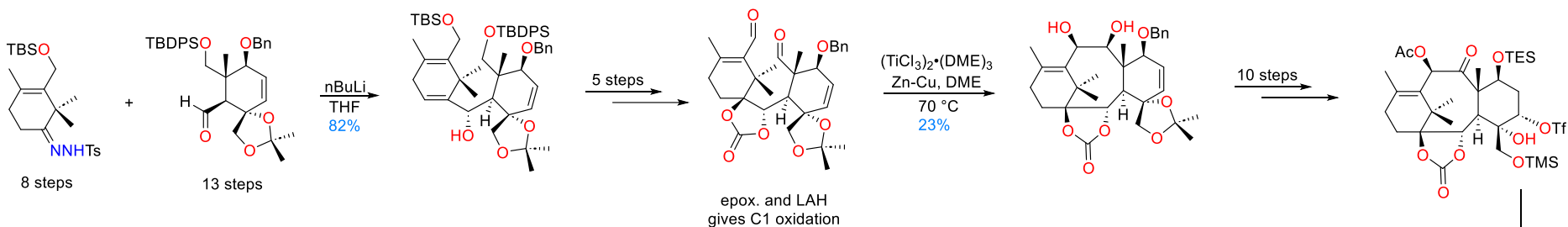
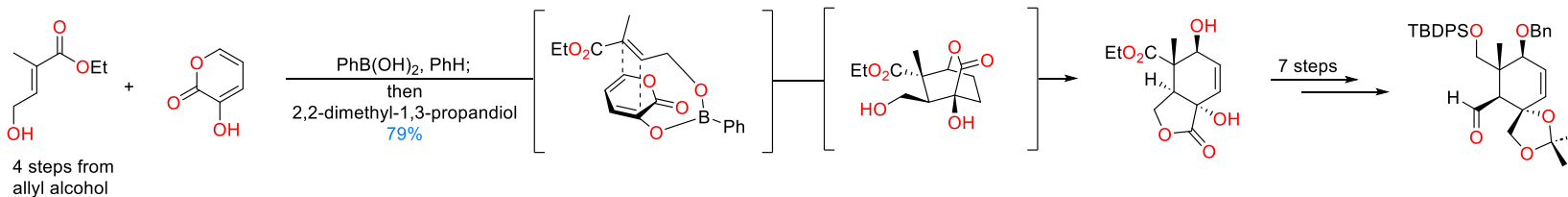
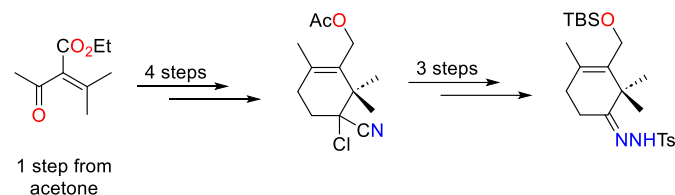


(-)-Taxol

Note: see slide 13 for references



- 40 steps LLS
- 3 year campaign
- enantiomeric synthesis by chiral separation
- 13.9 mg synthesized
- convergent



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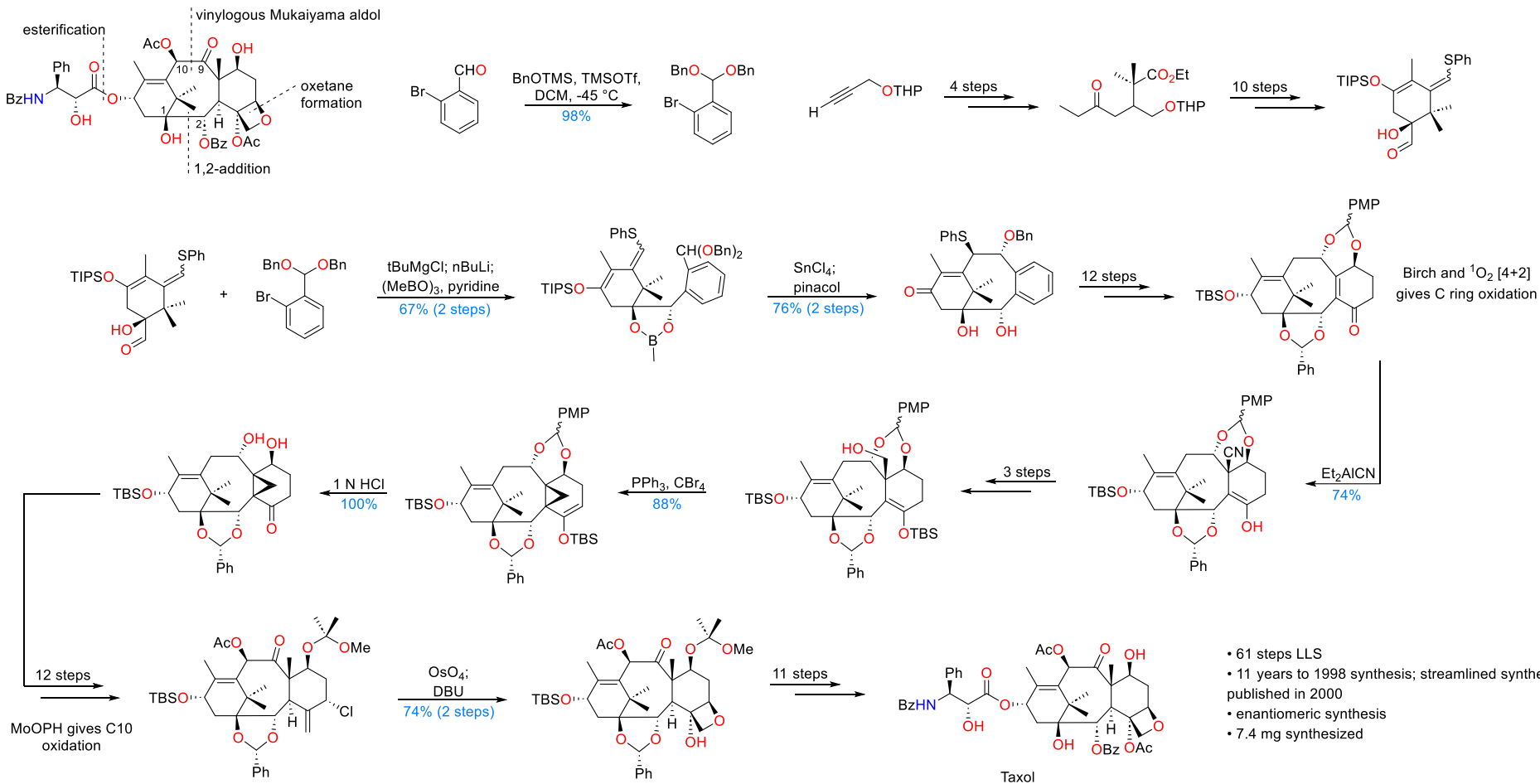
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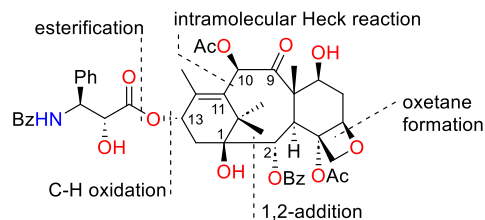


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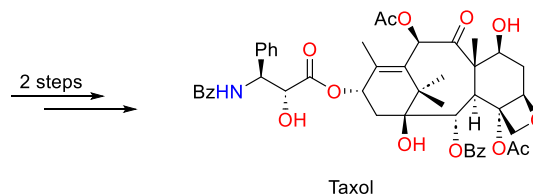
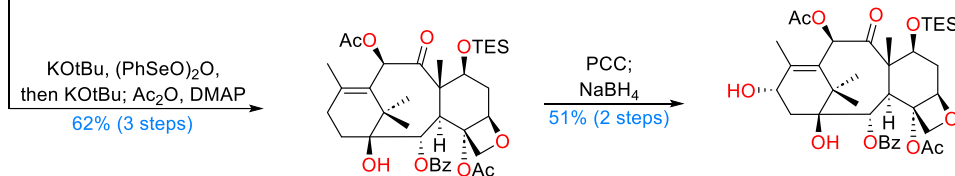
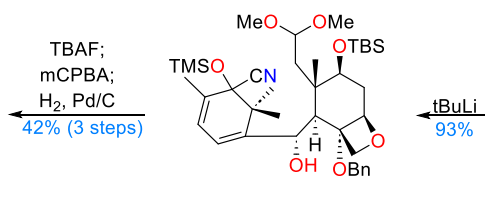
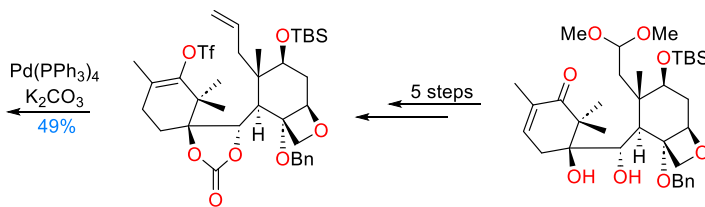
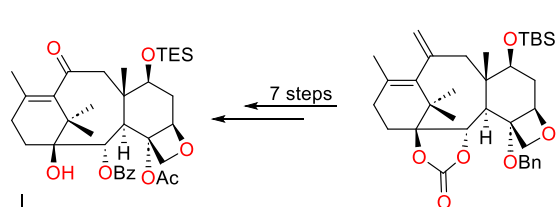
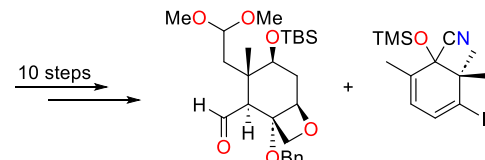
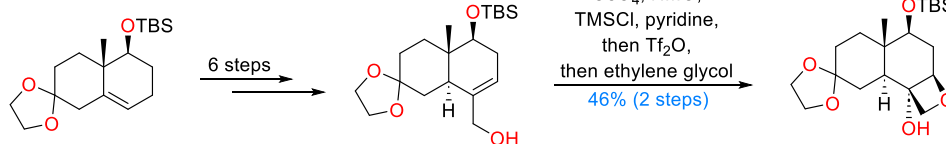
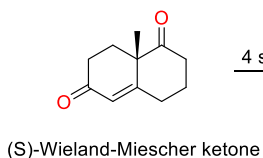
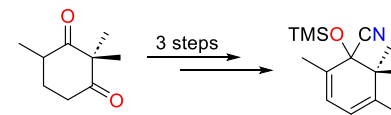
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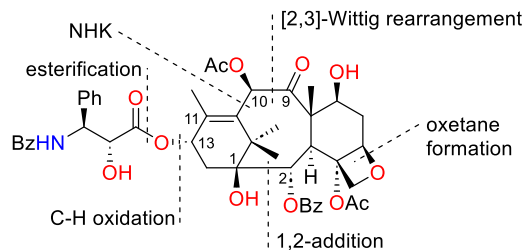


- 52 steps LLS
- 3 year campaign
- enantiomeric synthesis by chiral pool strategy
- early stage oxetane formation

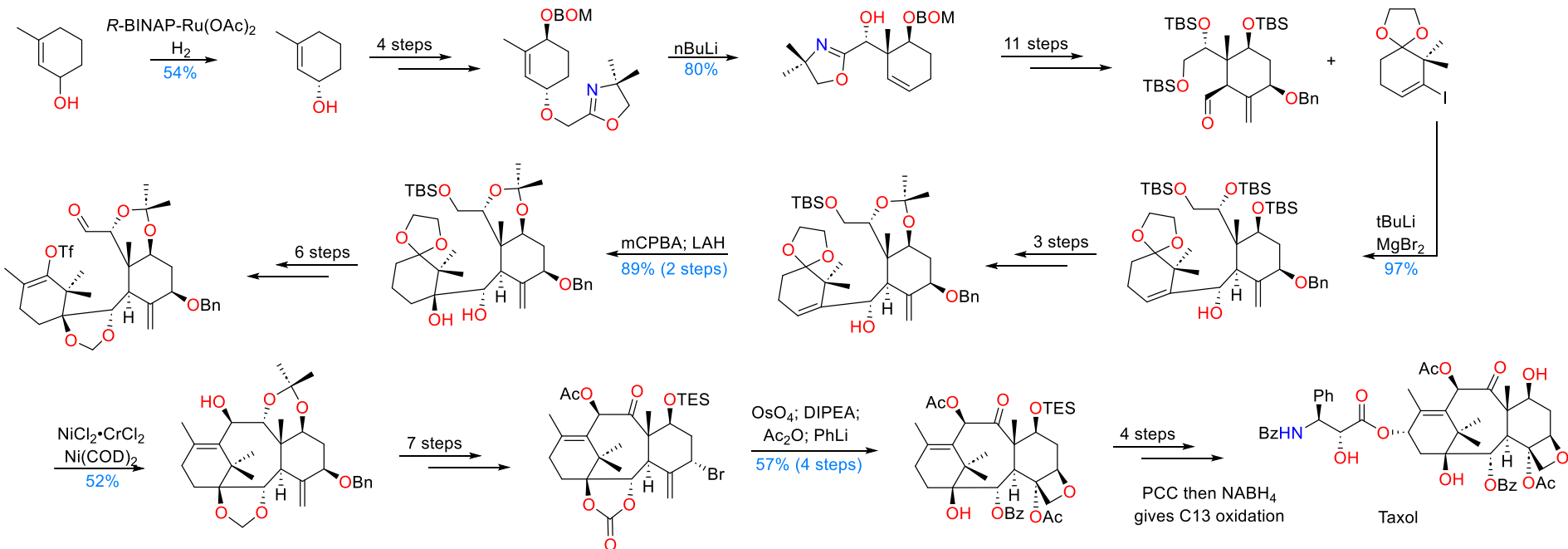
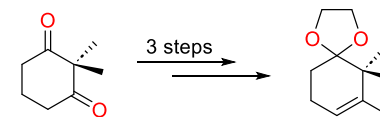


tBuLi
93%

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- 45 steps LLS
- 7 year campaign
- enantiomeric synthesis by chiral separation
- 2.9 mg synthesized



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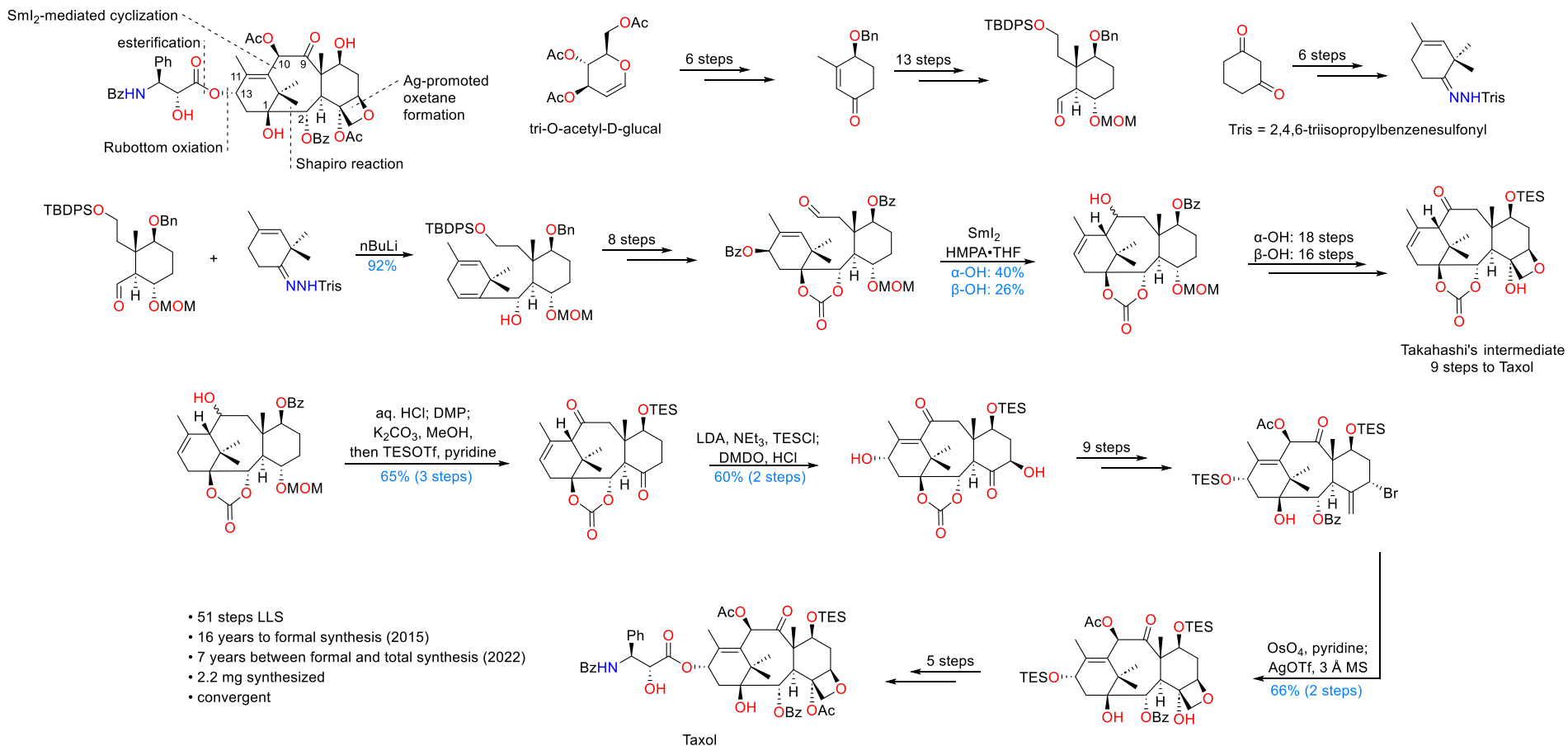
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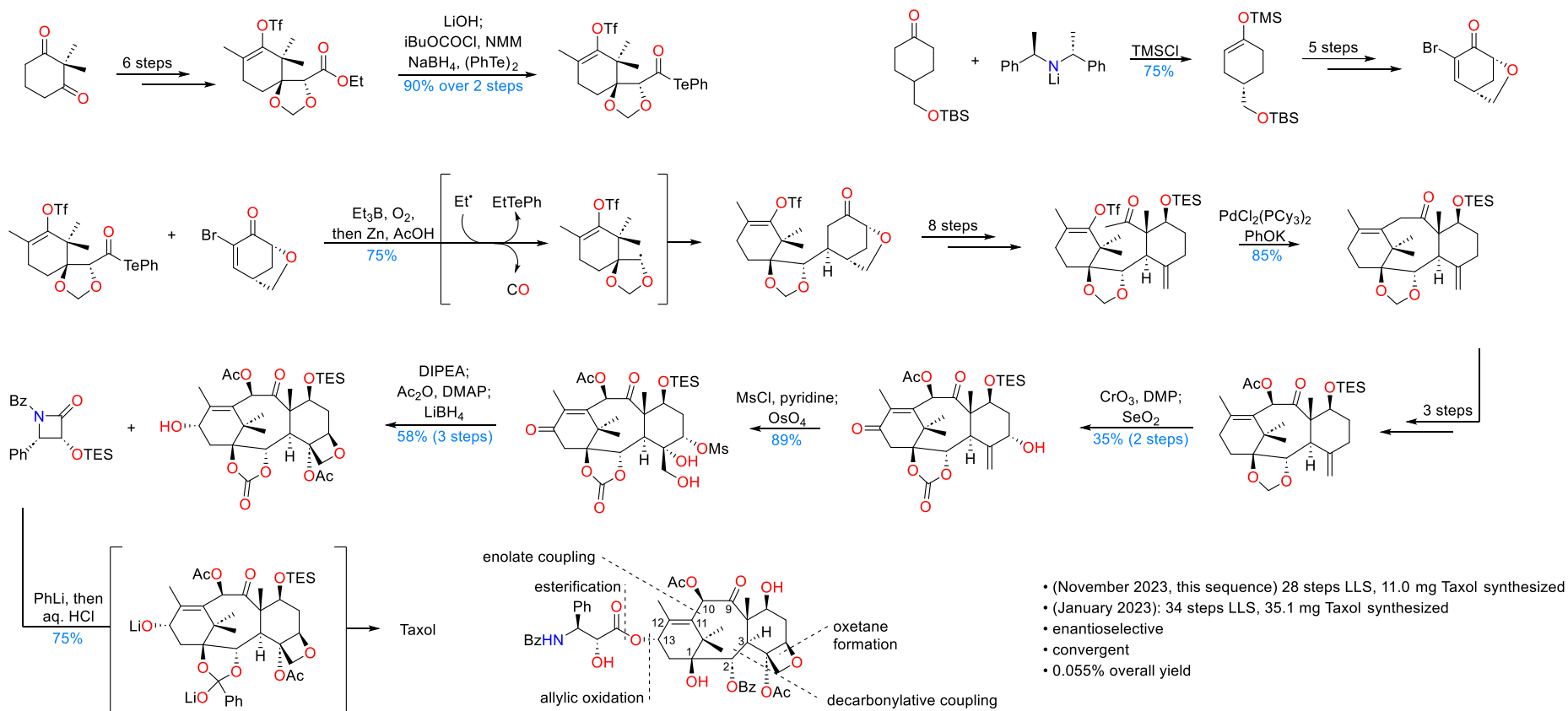
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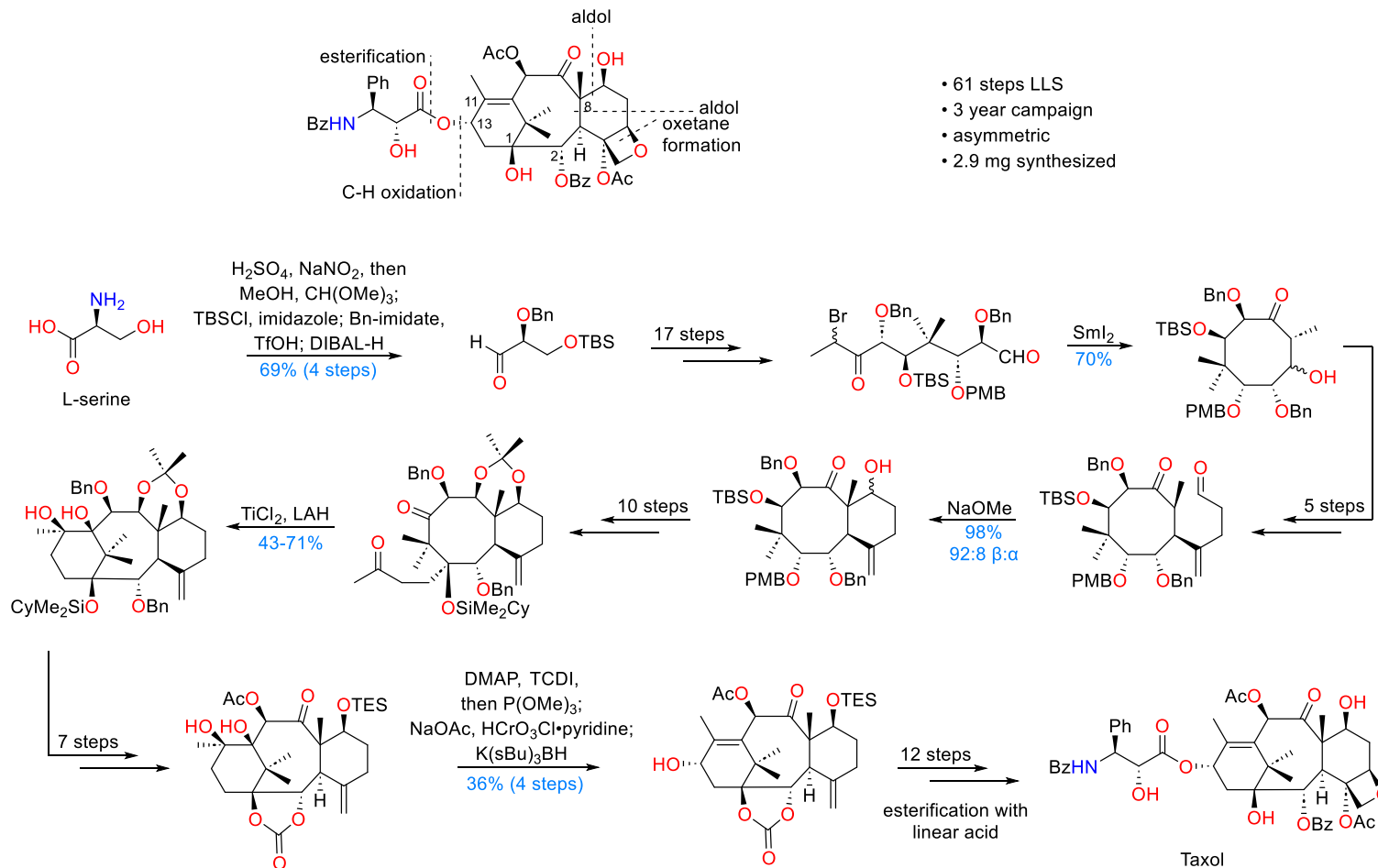


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 Hu, Y.-J., et al. *J. Am. Chem. Soc.* **2021**, 143, 42, 17862–17870. <https://doi.org/10.1021/jacs.1c09637>



- (November 2023, this sequence) 28 steps LLS, 11.0 mg Taxol synthesized
- (January 2023): 34 steps LLS, 35.1 mg Taxol synthesized
- enantioselective
- convergent
- 0.055% overall yield

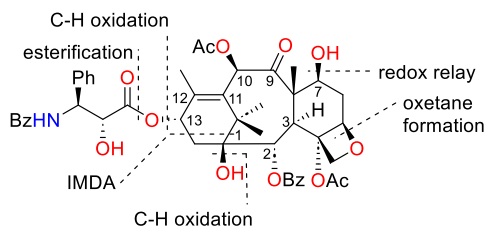
Mukaiyama (1997)



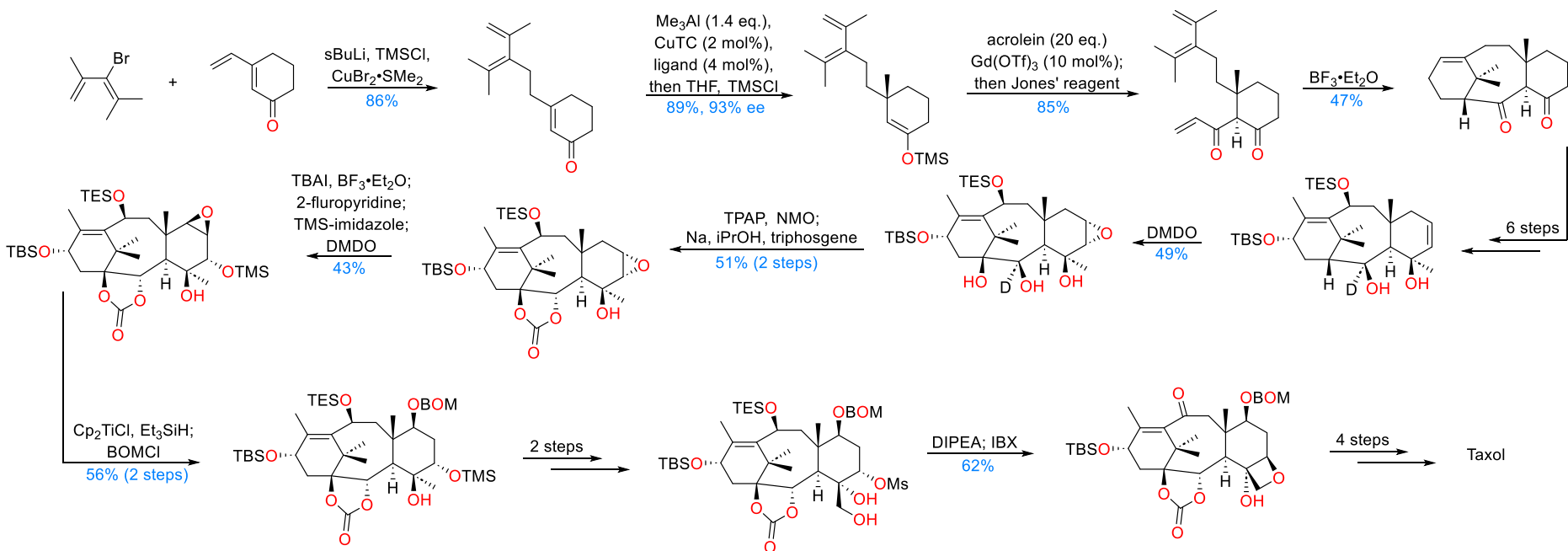
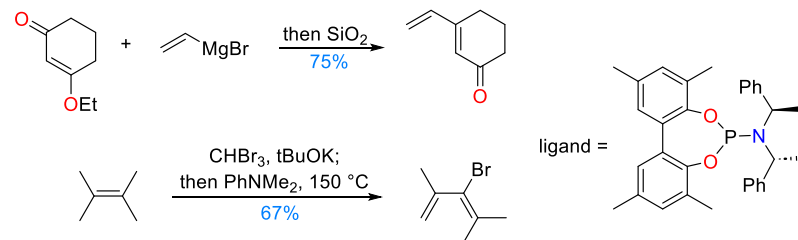
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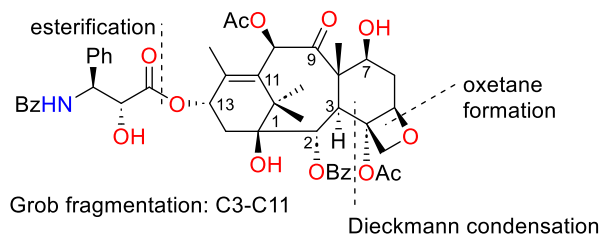
- 24 steps LLS
- 0.0014% overall yield
- synthesis of taxane skeleton: Nature, 2011
- divergent, biomimetic, two-phase synthesis
- 35.2 mg synthetic Taxol prepared



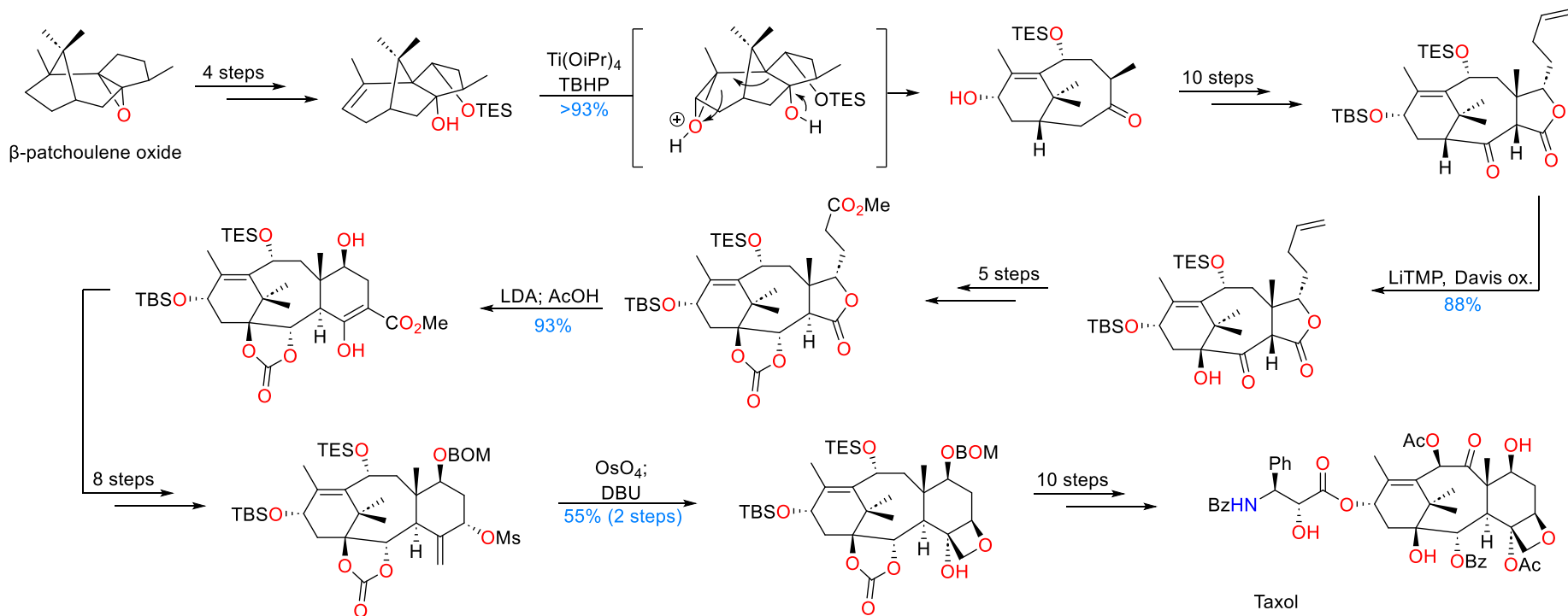
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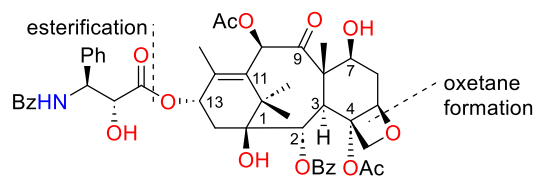
Hu, Y.-J., et al. *J. Am. Chem. Soc.* **2021**, 143, 42, 17862–17870. <https://doi.org/10.1021/jacs.1c09637>



- first Taxol total synthesis
- 46 steps LLS
- enantiomeric synthesis by chiral pool strategy
- 11.9 mg synthesized

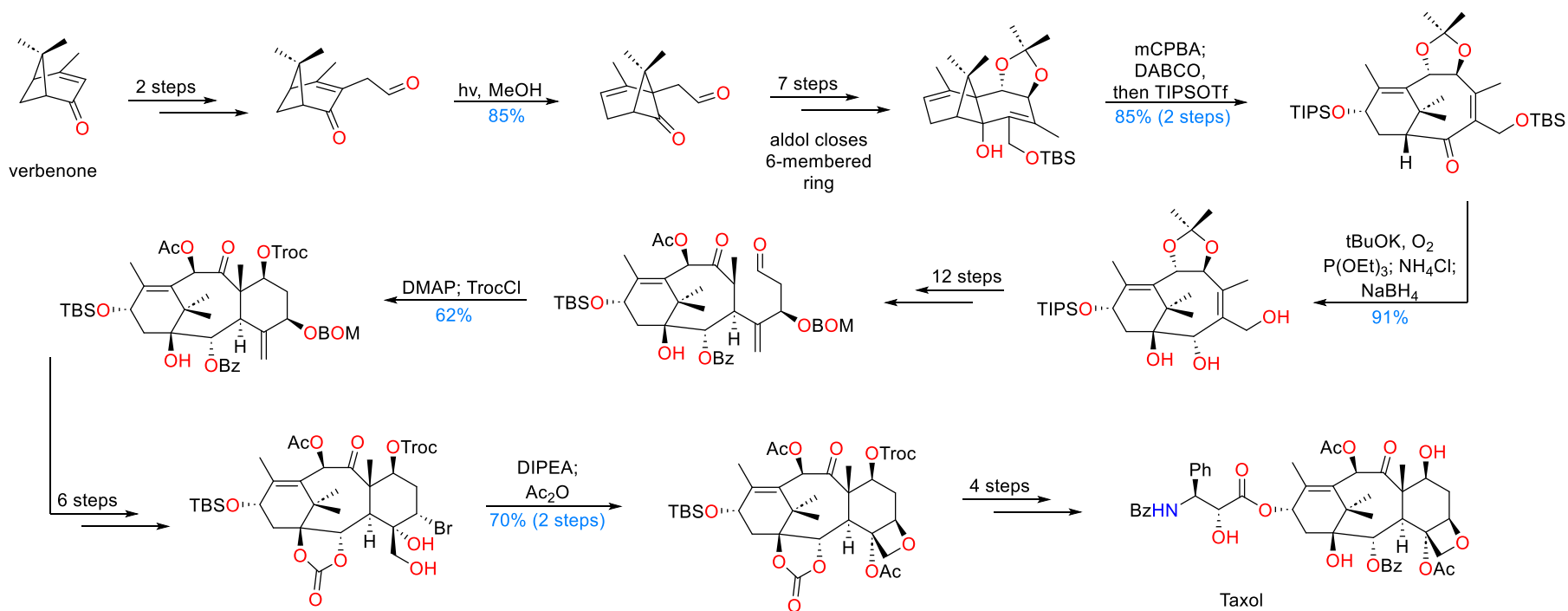


Holton, R. A., et al. *J. Am. Chem. Soc.* **1994**, 116, 1597–1598. <https://doi.org/10.1021/ja00083a066>
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 Hu, Y.-J., et al. *J. Am. Chem. Soc.* **2021**, 143, 42, 17862–17870. <https://doi.org/10.1021/jacs.1c09637>



Grob fragmentation: C3-C11

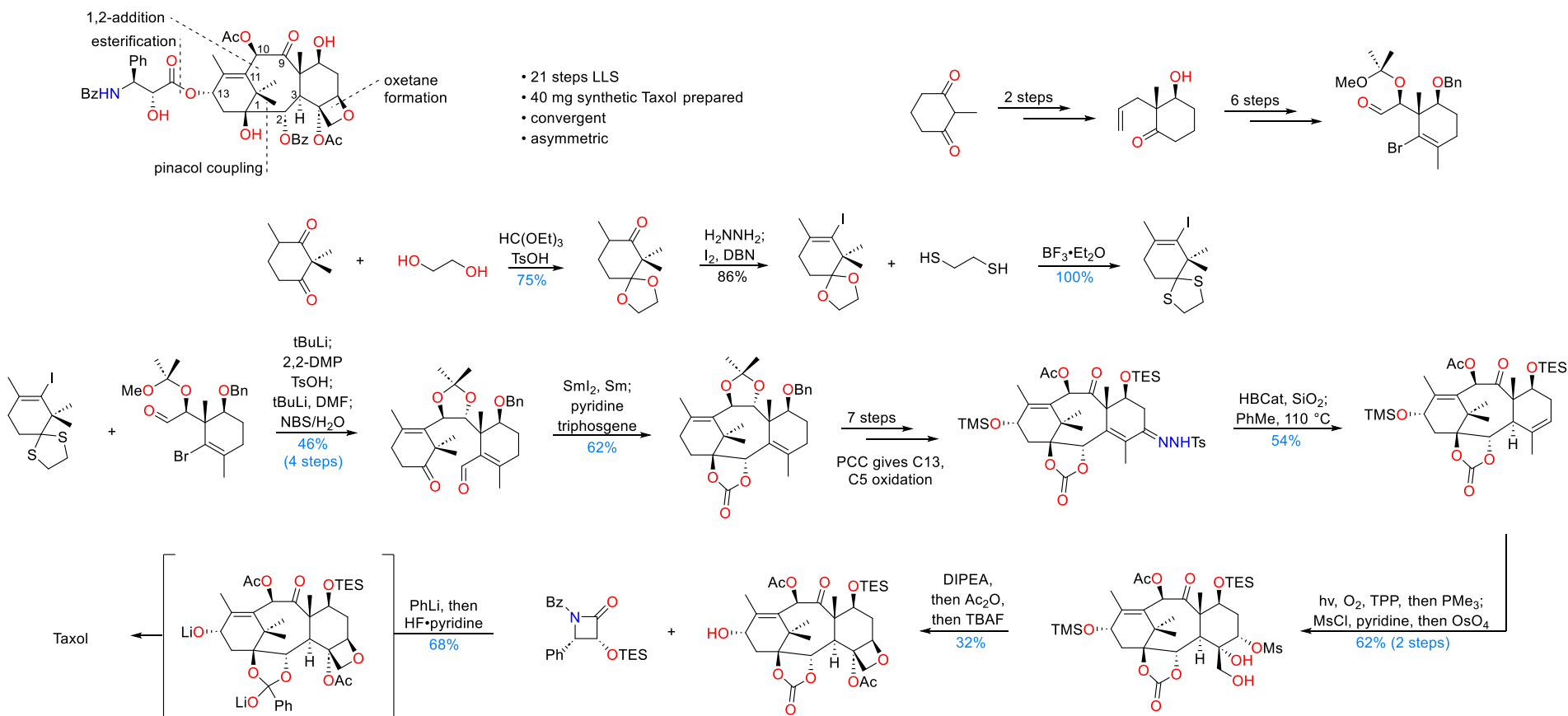
- formal synthesis: 38 steps LLS to intermediate 3 steps removed from target
- 10 years from first publication toward taxanes
- enantiomeric synthesis by chiral pool strategy



Wender, P. A., et al. *J. Am. Chem. Soc.* **1997**, 119, 2755–2756. <https://doi.org/10.1021/ja9635387>

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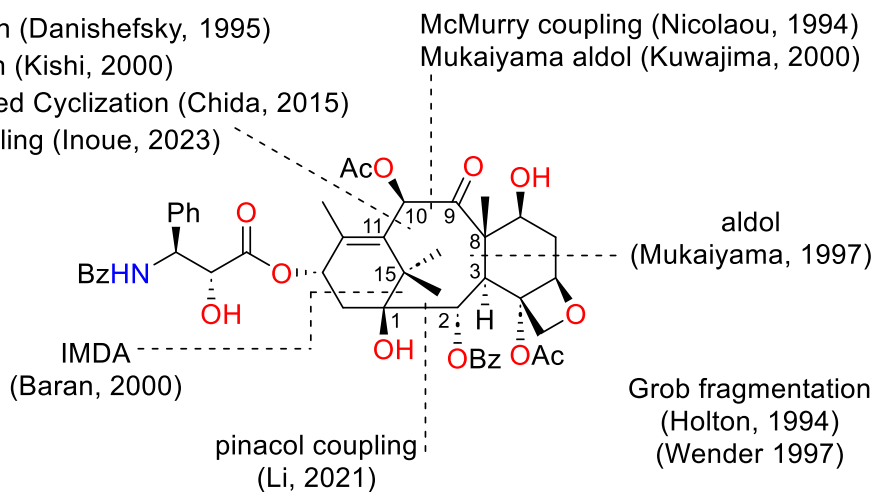
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 Hu, Y.-J., et al. *J. Am. Chem. Soc.* **2021**, 143, 42, 17862–17870. <https://doi.org/10.1021/jacs.1c09637>

Conclusions

- Taxol's total synthesis remains an academic-level pursuit
 - Taxol supply is a solved problem
- Taxol limitations: toxicity, poor solubility, drug resistance
- Nonetheless, its total synthesis illustrates the power of de novo total synthesis as a science and as an art
- 550 known taxane diterpenes, only a few of which have yielded to total synthesis, would benefit greatly from the chemistry developed in pursuit of Taxol and related taxanes



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