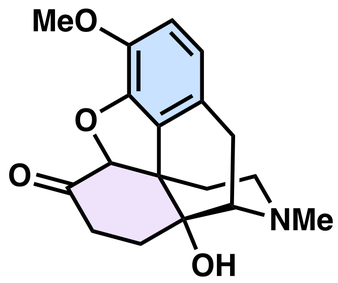
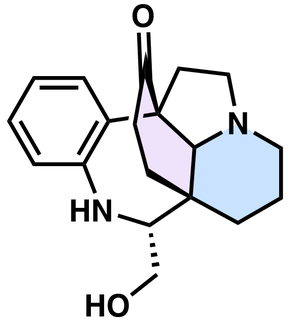
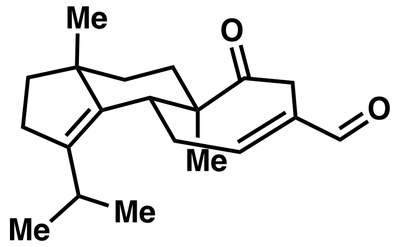
From Hidden Symmetry to Stereochemical Complexity



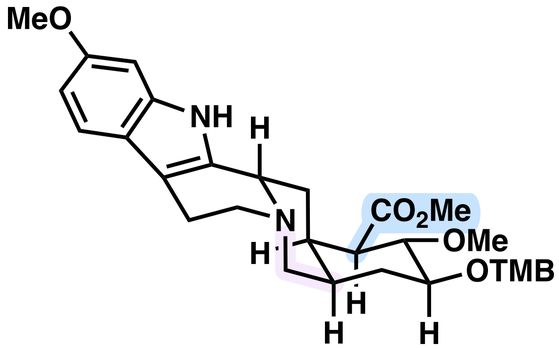
oxycodone



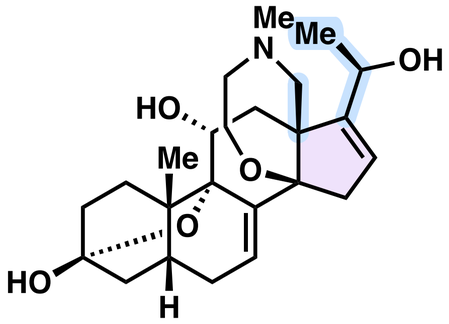
hunterin A



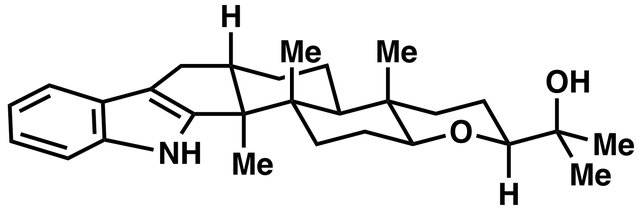
cyathin B_2



reserpine



batrachotoxinin A



paspaline

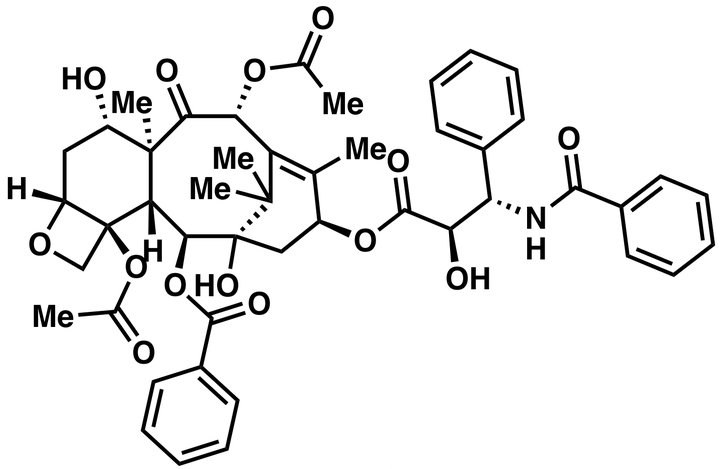
Myungeun Jeong

Literature talk

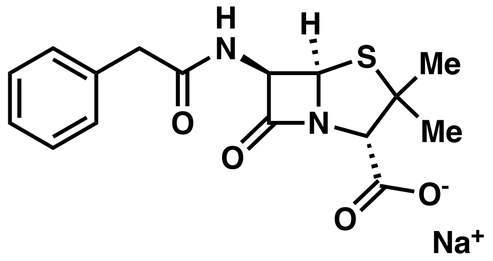
Apr, 10, 2026

SORENSEN LAB

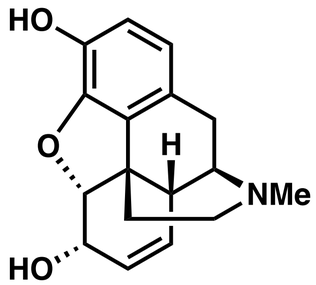
Stereochemical complexity in natural products



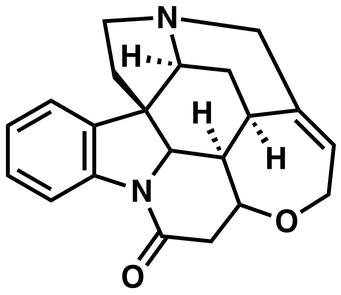
taxol



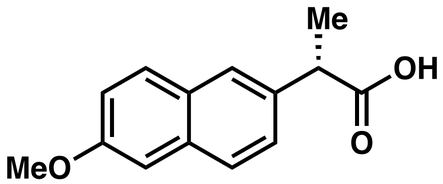
penicilin



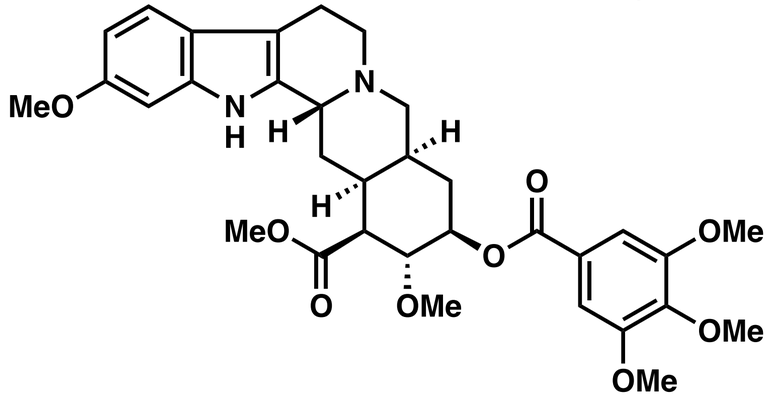
morphine



strychnine



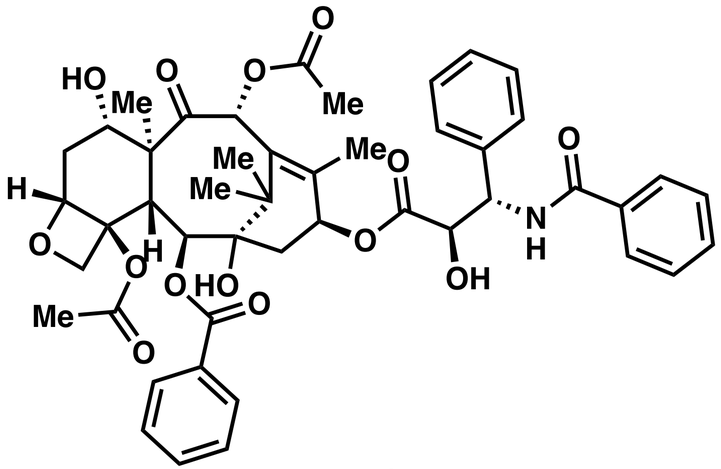
naproxen



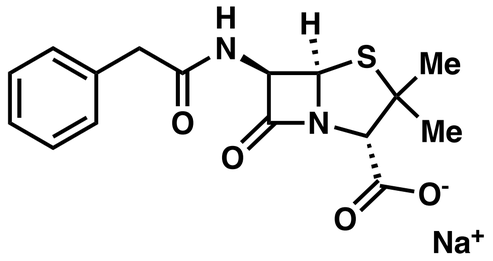
reserpine

- Many natural products contain multiple stereocenters and densely functionalized frameworks

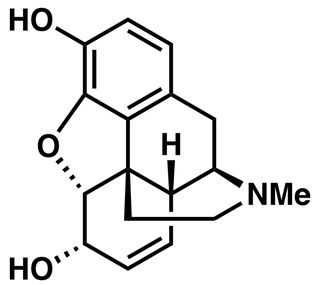
Stereochemical complexity in natural products



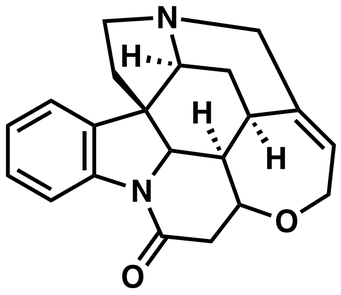
taxol



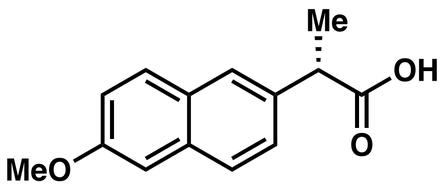
penicilin



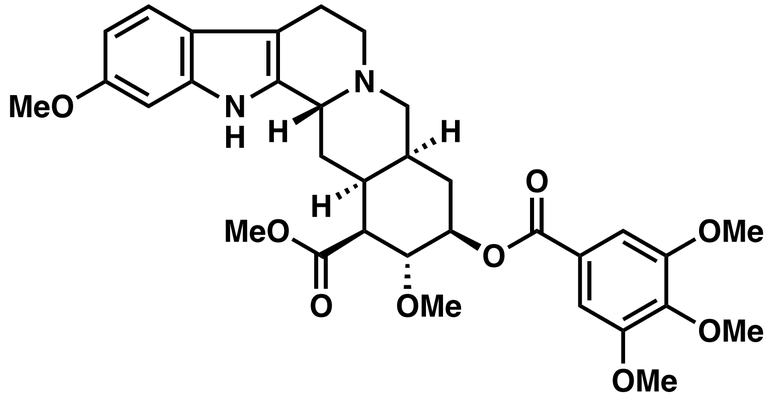
morphine



strychnine



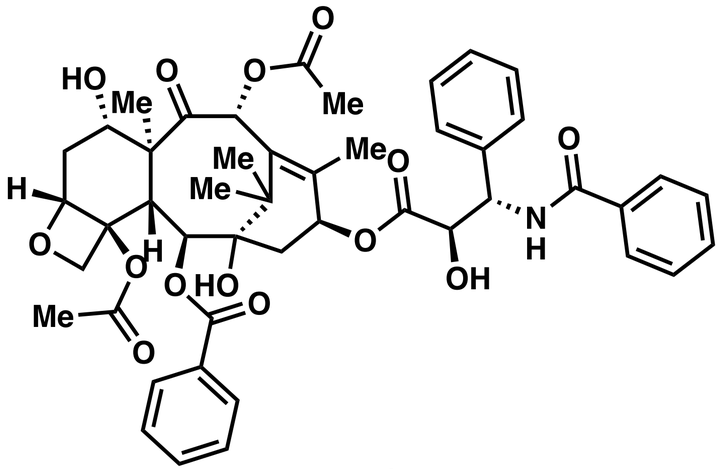
naproxen



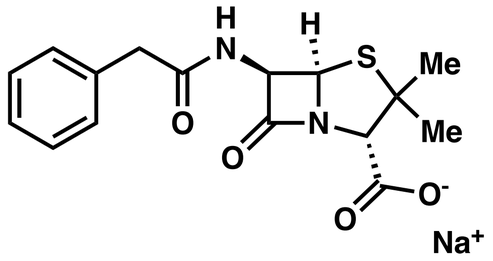
reserpine

- Many natural products contain multiple stereocenters and densely functionalized frameworks
- Controlling stereochemistry is a central challenge in total synthesis

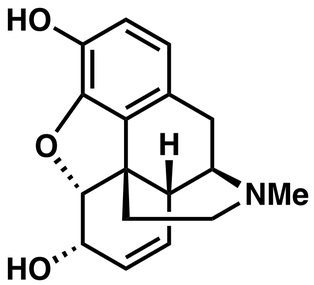
Stereochemical complexity in natural products



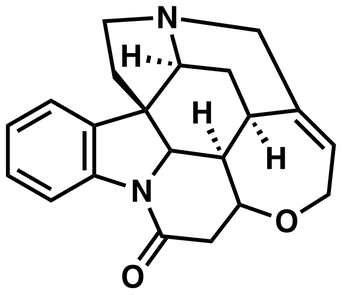
taxol



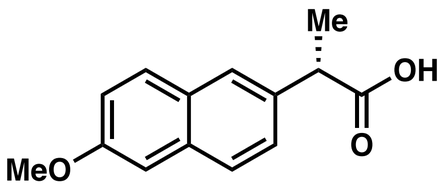
penicillin



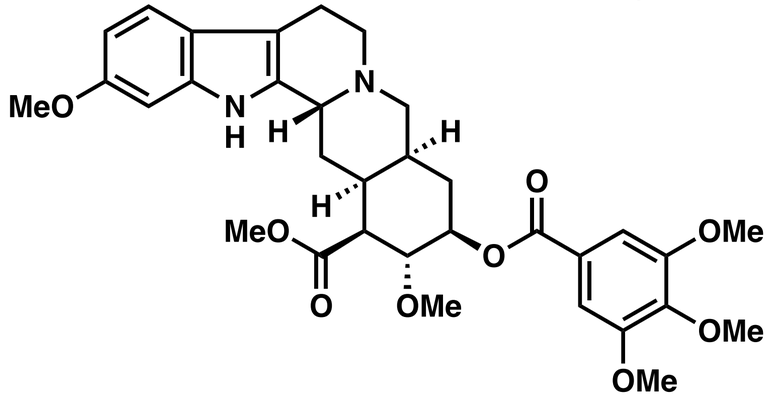
morphine



strychnine



naproxen

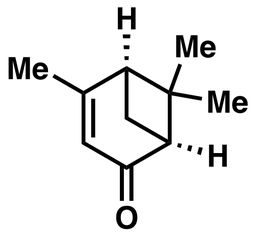


reserpine

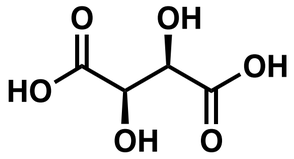
- Many natural products contain multiple stereocenters and densely functionalized frameworks
- Controlling stereochemistry is a central challenge in total synthesis
- This challenge has driven the development of asymmetric synthetic strategies

One classical solution: Chiral pool synthesis

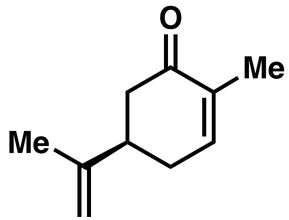
- Chiral pool synthesis uses naturally occurring chiral starting materials
- Generally abundant, inexpensive, and readily available
- Their pre-existing stereochemistry is carried into the target



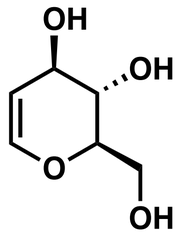
(-)-verbeone



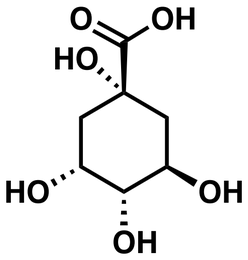
tartaric acid



L-carvone



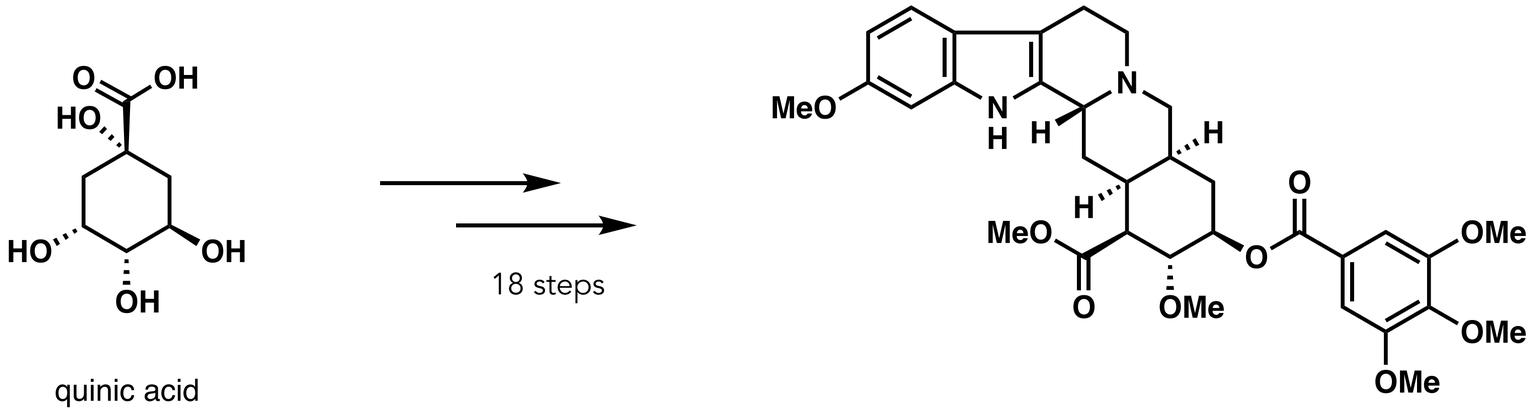
D-glucal



quinic acid

One classical solution: Chiral pool synthesis

- Chiral pool synthesis uses naturally occurring chiral starting materials
- Generally abundant, inexpensive, and readily available
- Their pre-existing stereochemistry is carried into the target
- Example: quinic acid in reserpine synthesis



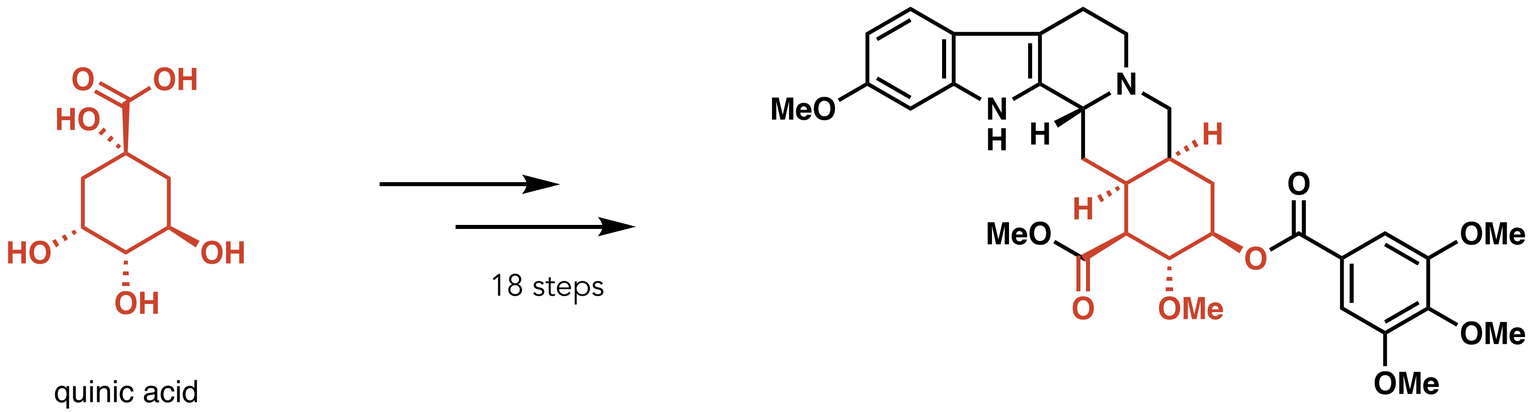
quinic acid

reserpine

Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004

One classical solution: Chiral pool synthesis

- Chiral pool synthesis uses naturally occurring chiral starting materials
- Generally abundant, inexpensive, and readily available
- Their pre-existing stereochemistry is carried into the target
- Example: quinic acid in reserpine synthesis



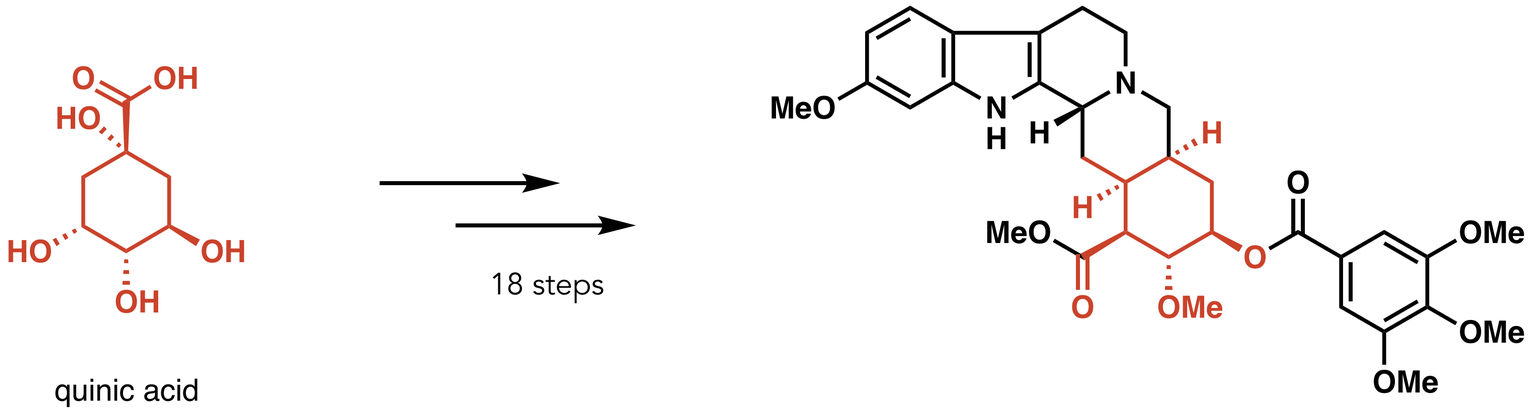
quinic acid

reserpine

Hanessian, S.; Pan, J.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997,** *62*, 465–473.

One classical solution: Chiral pool synthesis

- Chiral pool synthesis uses naturally occurring chiral starting materials
- Generally abundant, inexpensive, and readily available
- Their pre-existing stereochemistry is carried into the target
- Suitable chiral starting materials are not always available
- Their intirinsic stereochemistry may not match the target
- This could reduce flexibility in route design



quinic acid

reserpine

Hanessian, S.; Pan, J.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997,** *62*, 465–473.

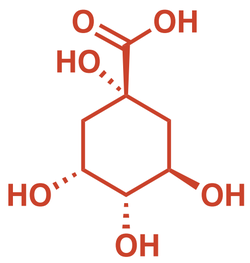
Another strategies: Desymmetrization

- Begin with a symmetric precursor
- Selective differentiation of originally equivalent groups breaks symmetry by creating chirality

Hanessian, S.; Pan, J.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997,** *62*, 465–473.
Park, J.; Chen, D. Y. K. *Angew. Chem. Int. Ed.* **2018,** *57*, 16152–16156.

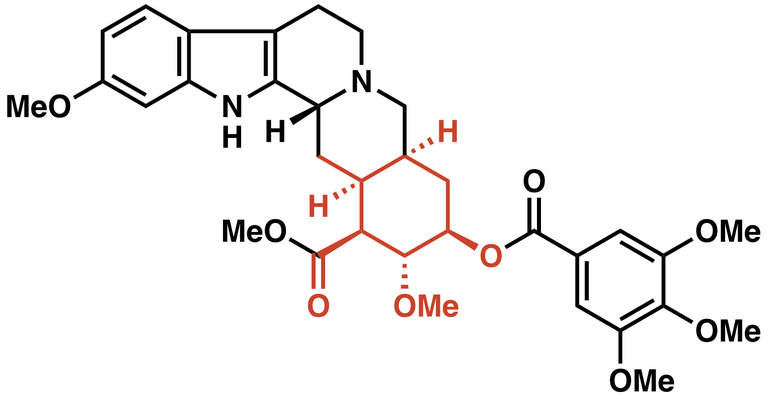
Another strategies: Desymmetrization

- Begin with a symmetric precursor
- Selective differentiation of originally equivalent groups breaks symmetry by creating chirality
- Example: quinic acid in reserpine synthesis



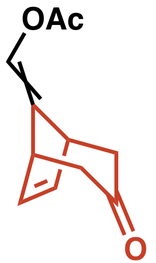
quinic acid

18 steps



reserpine

16 steps

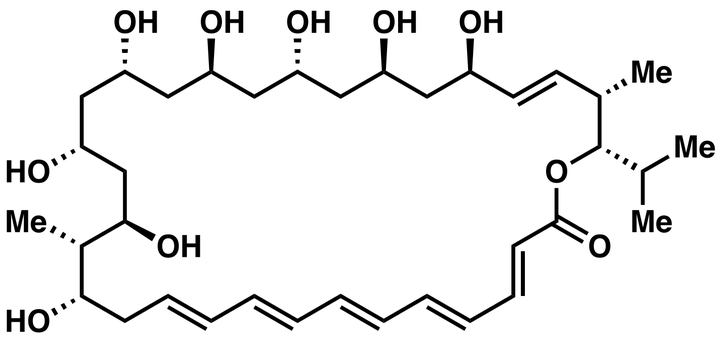


prepared from
tetrabromoacetone and acetoxyfulvene

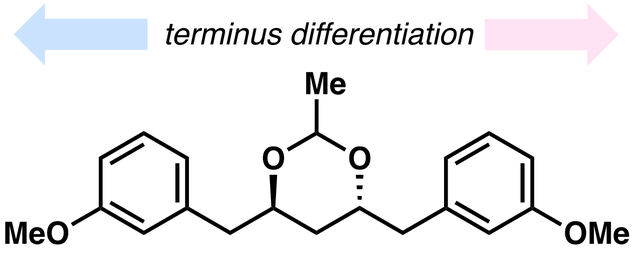
Hanessian, S.; Pan, J.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997,** *62*, 465–473.
Park, J.; Chen, D. Y. K. *Angew. Chem. Int. Ed.* **2018,** *57*, 16152–16156.

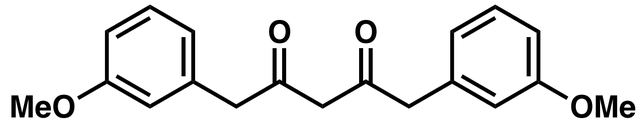
Why desymmetrization is powerful?

Utilizing Symmetry for Asymmetric Synthesis



mytoticin A

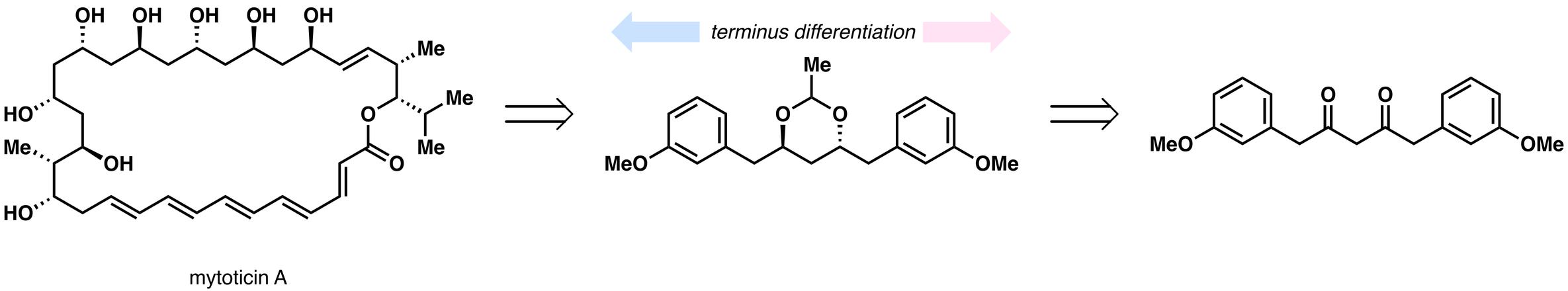




Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360–3361.
Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9–17.

Why desymmetrization is powerful?

Utilizing Symmetry for Asymmetric Synthesis



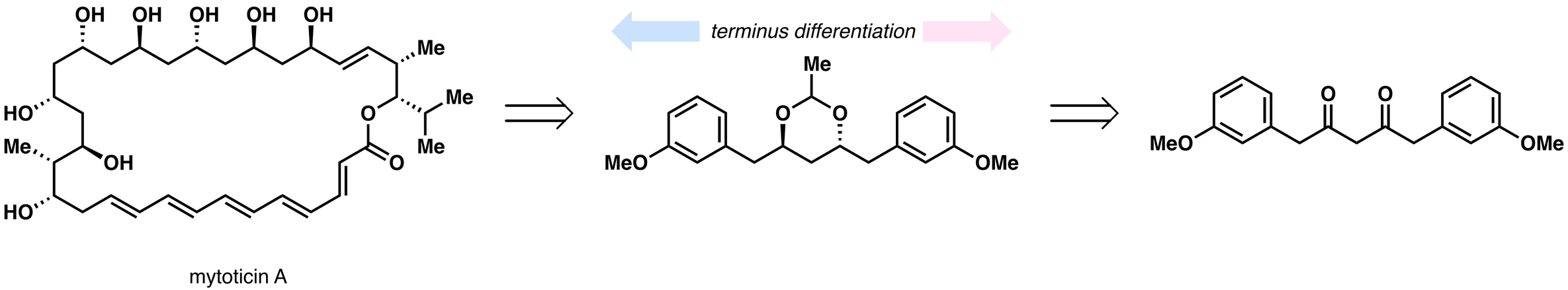
mytoticin A

- It allows scaffold assembly and chirality induction to be separated
- This enables efficient late-stage stereocontrol

Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360–3361.
Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9–17.

Why desymmetrization is powerful?

Utilizing Symmetry for Asymmetric Synthesis



mytoticin A

- It allows scaffold assembly and chirality induction to be separated
- This enables efficient late-stage stereocontrol
- Symmetric precursors are simple and readily available
- A single step can rapidly generate complex chiral architectures

Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360–3361.
Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9–17.

Hidden symmetry in desymmetrization

Desymmetrization starts by identifying hidden symmetry in the target molecule

Liu, H.; Tang, K.; Jia, Y.; *et al. Chem. Soc. Rev.* **2025,** *54*, 6208–6237.

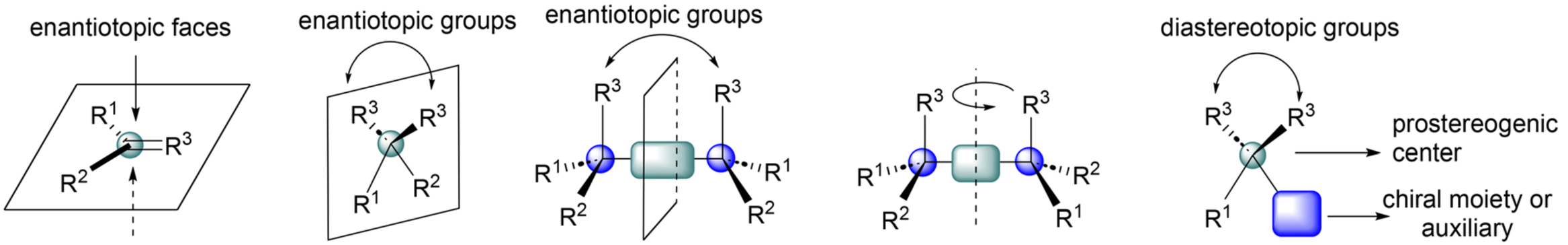
Hidden symmetry in desymmetrization

Desymmetrization starts by identifying hidden symmetry in the target molecule

Prochiral and meso compound

C2 symmetric compounds

local symmetric compound



Liu, H.; Tang, K.; Jia, Y.; *et al. Chem. Soc. Rev.* **2025,** *54*, 6208–6237.

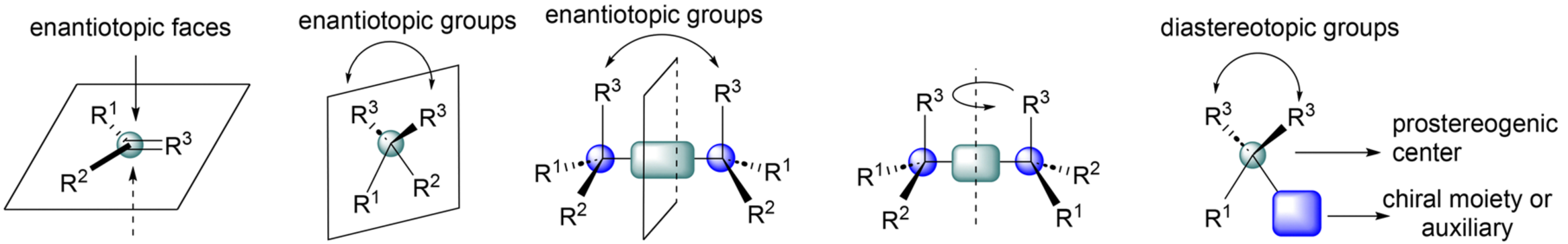
Hidden symmetry in desymmetrization

Desymmetrization starts by identifying hidden symmetry in the target molecule

Prochiral and meso compound

C2 symmetric compounds

local symmetic compound



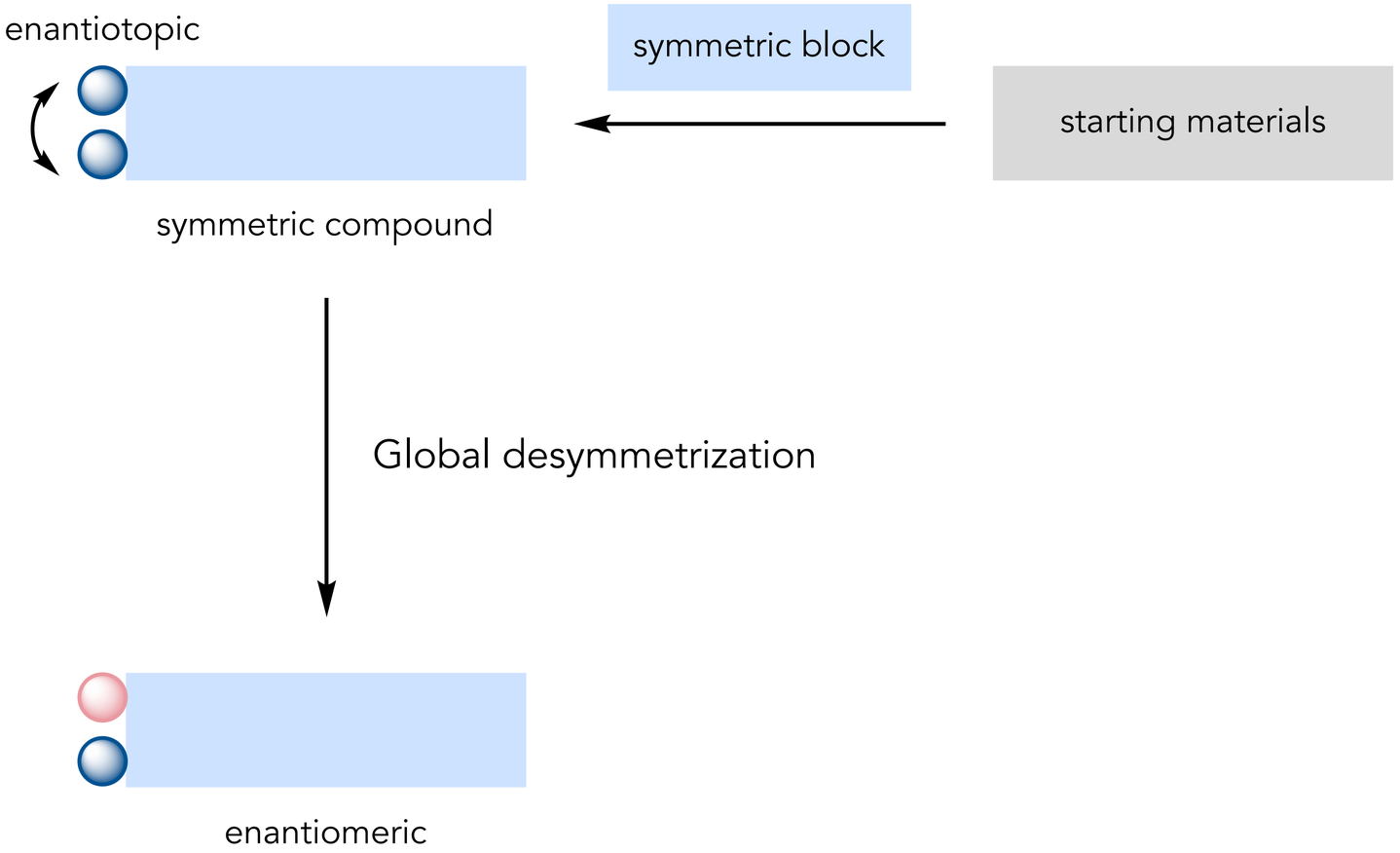
Enantiotopic group differentiation ➢ enantiomeric products

Diastereotopic group differentiation ➢ diastereomeric products

Liu, H.; Tang, K.; Jia, Y.; *et al. Chem. Soc. Rev.* **2025,** *54*, 6208–6237.

Global desymmetrization vs. Local desymmetrization

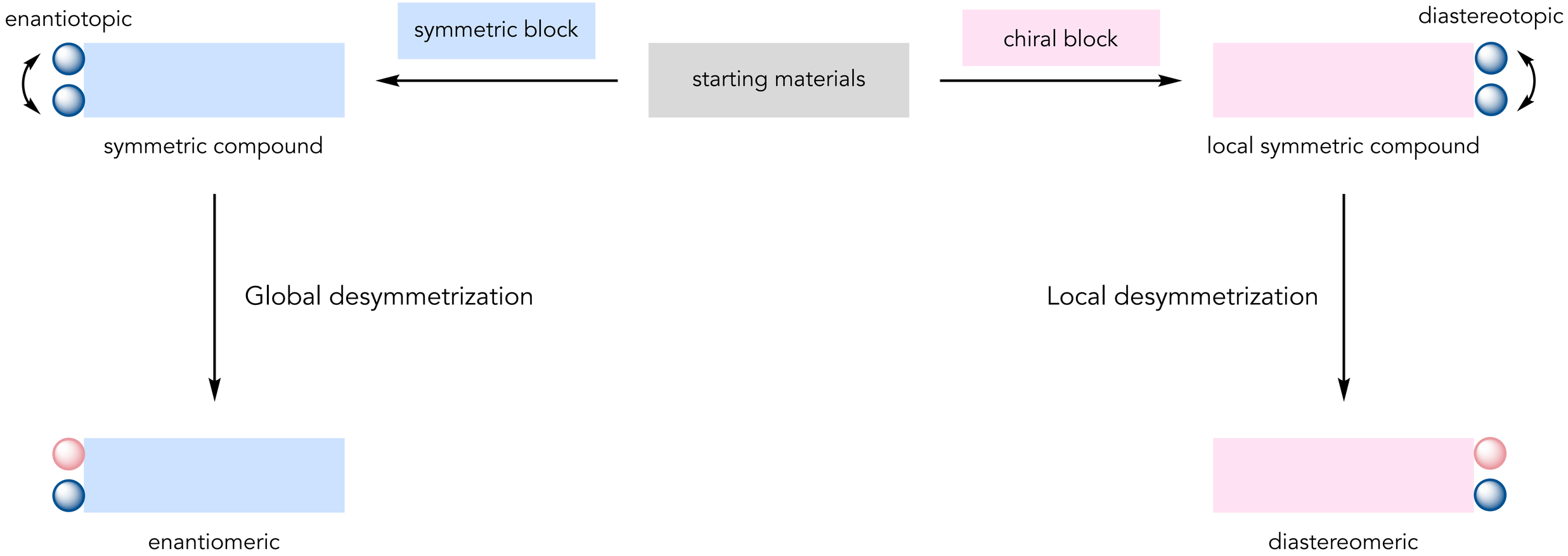
Enantiotopic group differentiation ➢ enantiomeric products
Diastereotopic group differentiation ➢ diastereomeric products



Liu, H.; Tang, K.; Jia, Y.; *et al. Chem. Soc. Rev.* **2025,** *54*, 6208–6237.

Global desymmetrization vs. Local desymmetrization

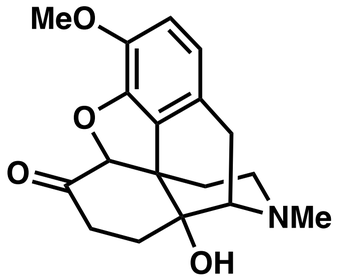
Enantiotopic group differentiation ➢ enantiomeric products
Diastereotopic group differentiation ➢ diastereomeric products



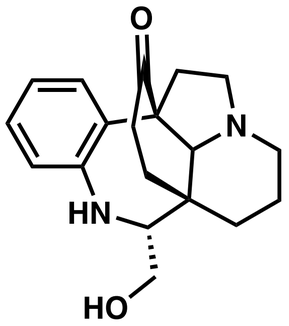
Liu, H.; Tang, K.; Jia, Y.; *et al. Chem. Soc. Rev.* **2025,** *54*, 6208–6237.

Overview

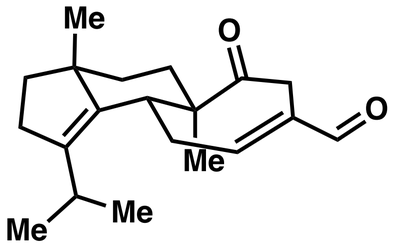
Global desymmetrization



oxycodone



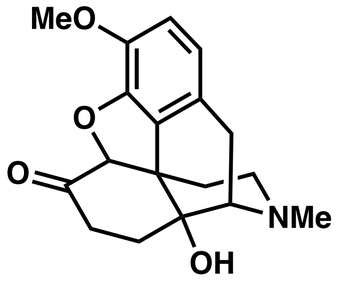
hunterin A



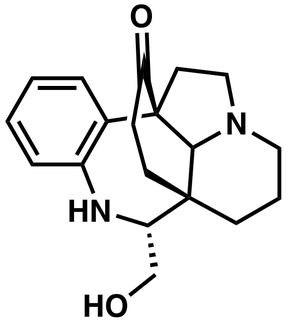
cyathin B_2

Overview

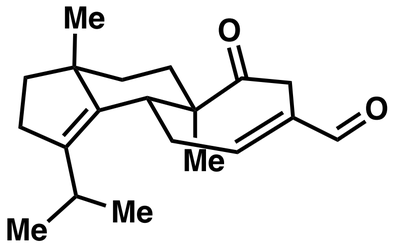
Global desymmetrization



oxycodone

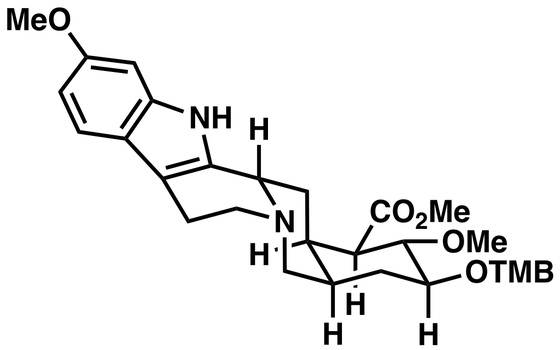


hunterin A

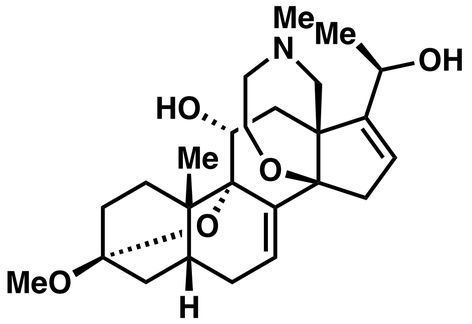


cyathin B_2

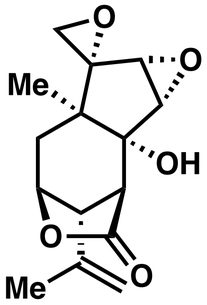
Local desymmetrization



reserpine



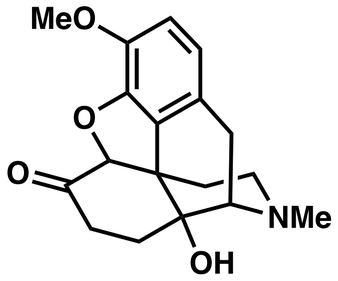
batrachotoxinin A



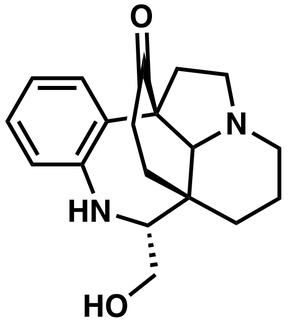
coriamyrtin

Overview

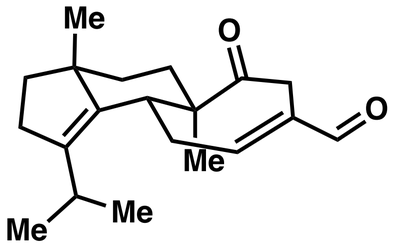
Global desymmetrization



oxycodone

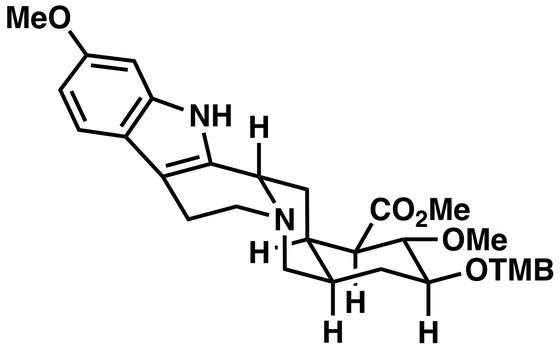


hunterin A

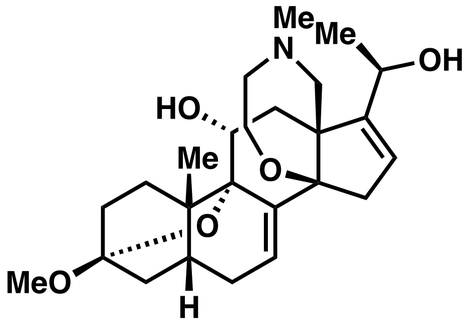


cyathin B_2

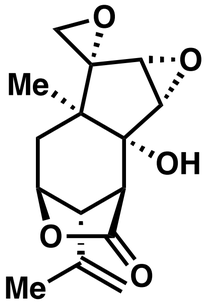
Local desymmetrization



reserpine

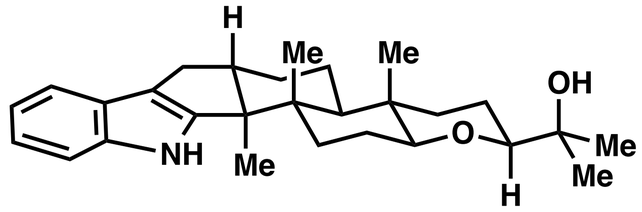


batrachotoxinin A

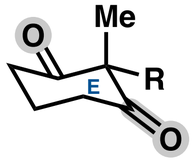


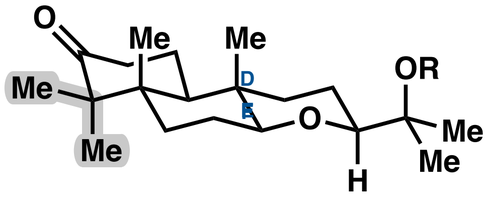
coriamyrtin

Combined global and local desymmetrization

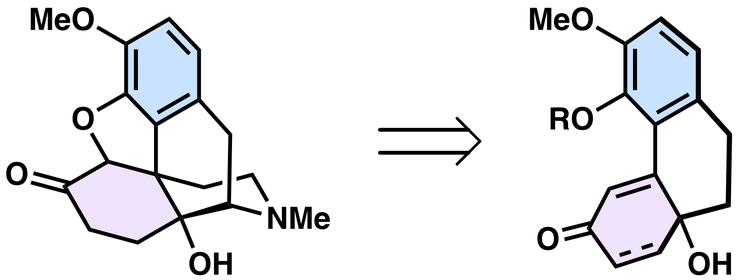


paspaline





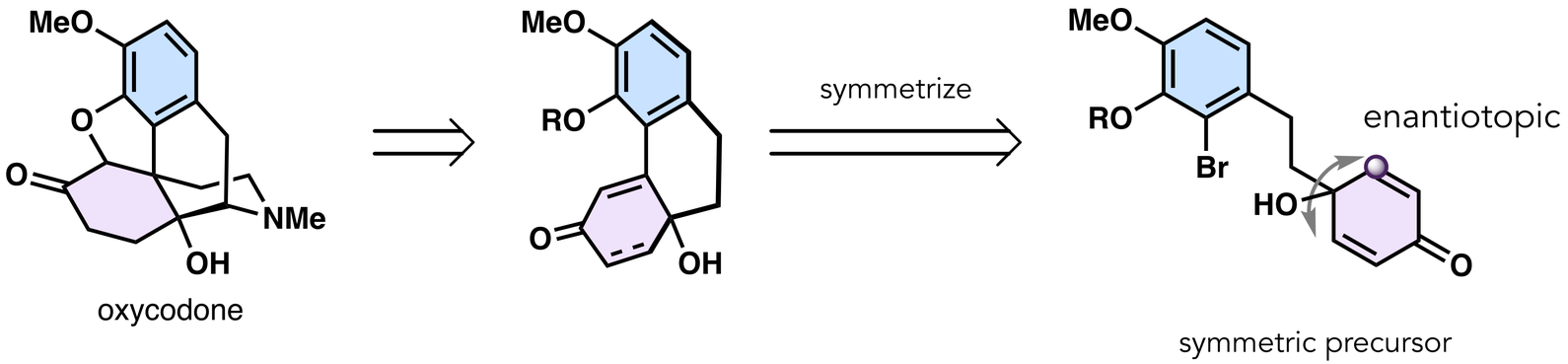
Oxycodone: Dienone Desymmetrization toward the Morphinan Framework



oxycodone

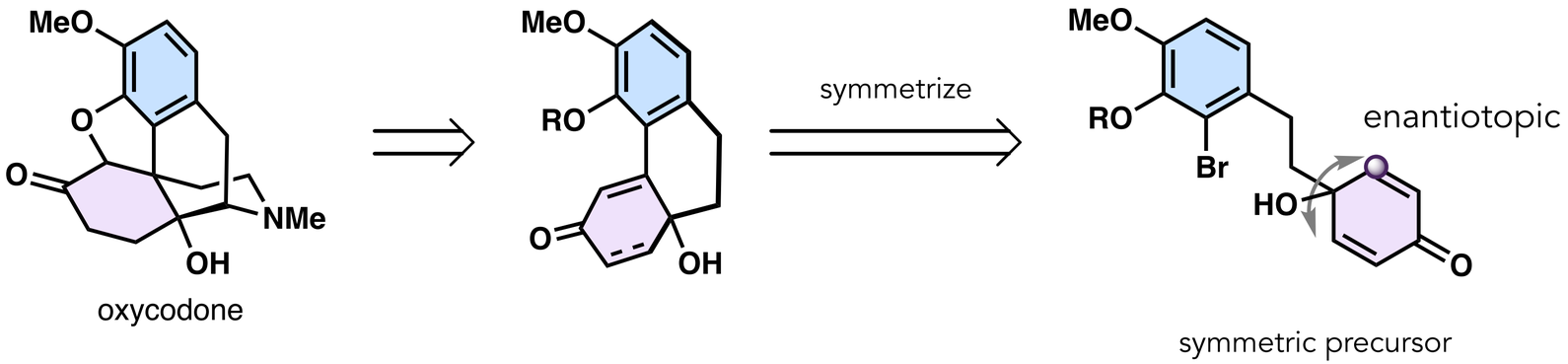
Park, K. H.; Chen, D. Y. K. *Chem. Commun.* **2018,** *54*, 13018–13021.

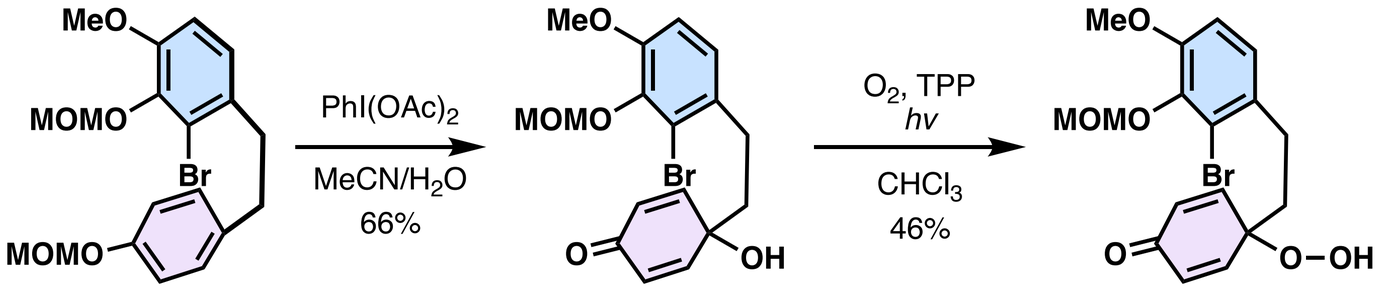
Oxycodone: Dienone Desymmetrization toward the Morphinan Framework



Park, K. H.; Chen, D. Y. K. *Chem. Commun.* **2018,** *54*, 13018–13021.

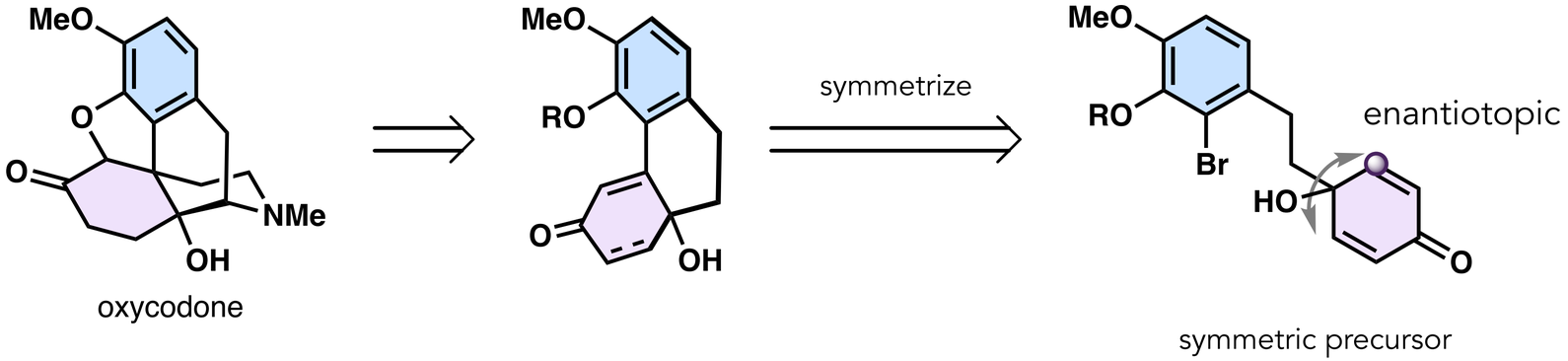
Oxycodone: Dienone Desymmetrization toward the Morphinan Framework

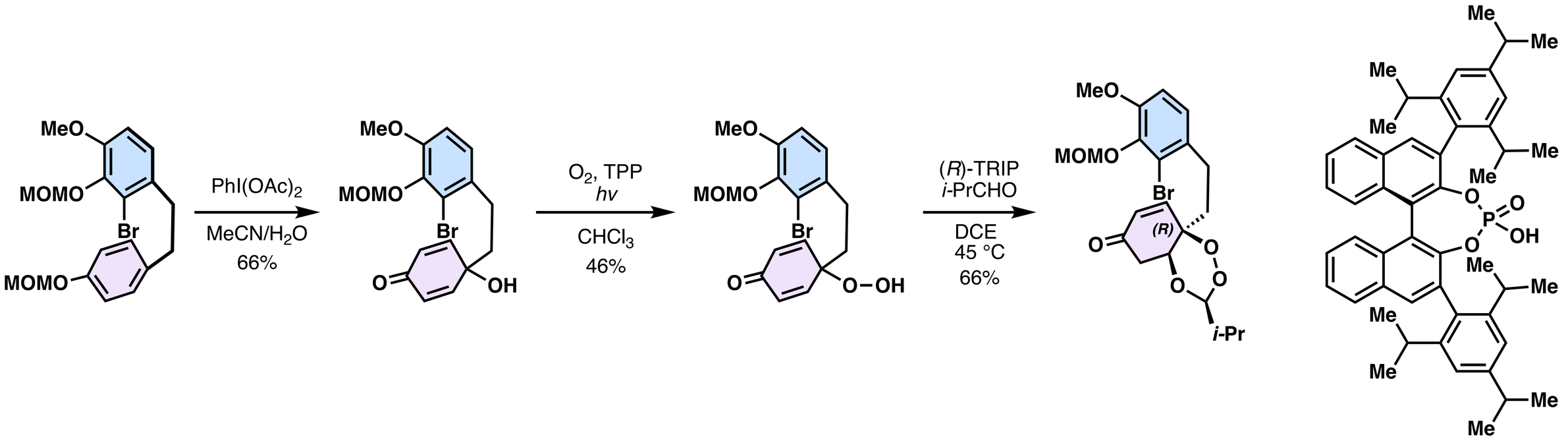




Park, K. H.; Chen, D. Y. K. *Chem. Commun.* **2018,** *54*, 13018–13021.

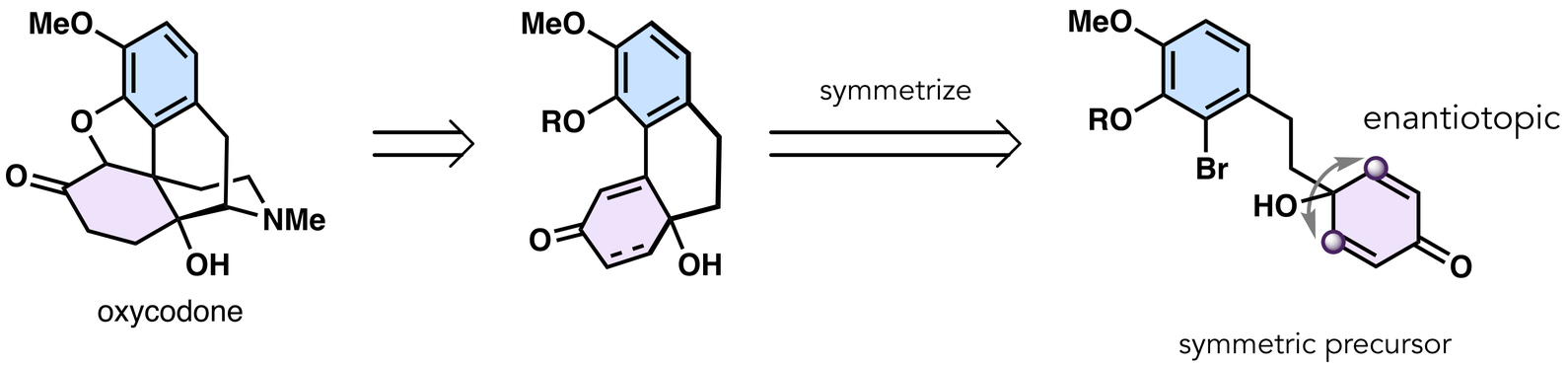
Oxycodone: Dienone Desymmetrization toward the Morphinan Framework

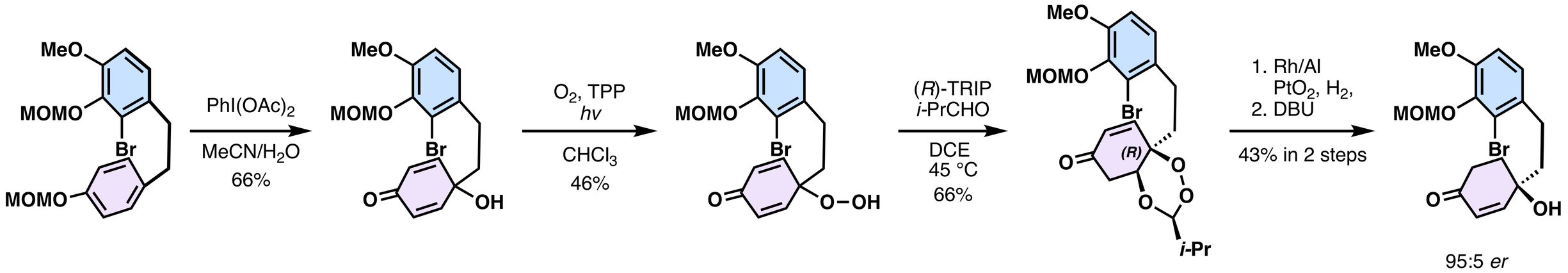




Park, K. H.; Chen, D. Y. K. *Chem. Commun.* **2018,** *54*, 13018–13021.

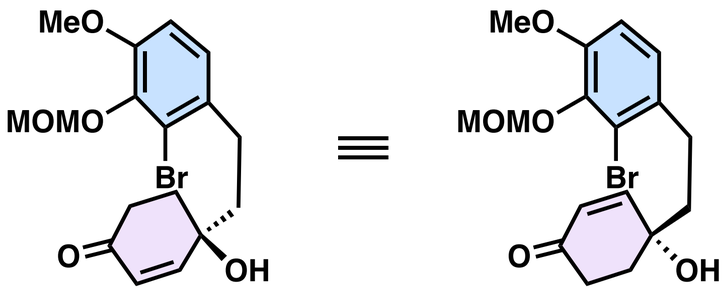
Oxycodone: Dienone Desymmetrization toward the Morphinan Framework





Park, K. H.; Chen, D. Y. K. *Chem. Commun.* **2018,** *54*, 13018–13021.

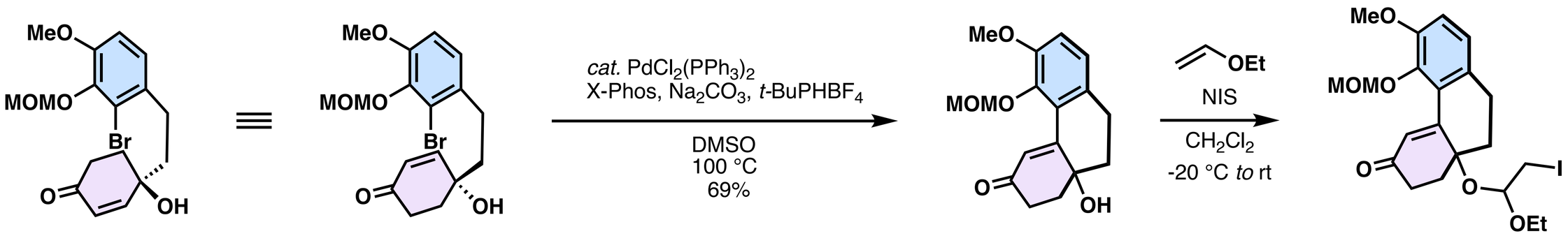
Oxycodone: Dienone Desymmetrization toward the Morphinan Framework



≡

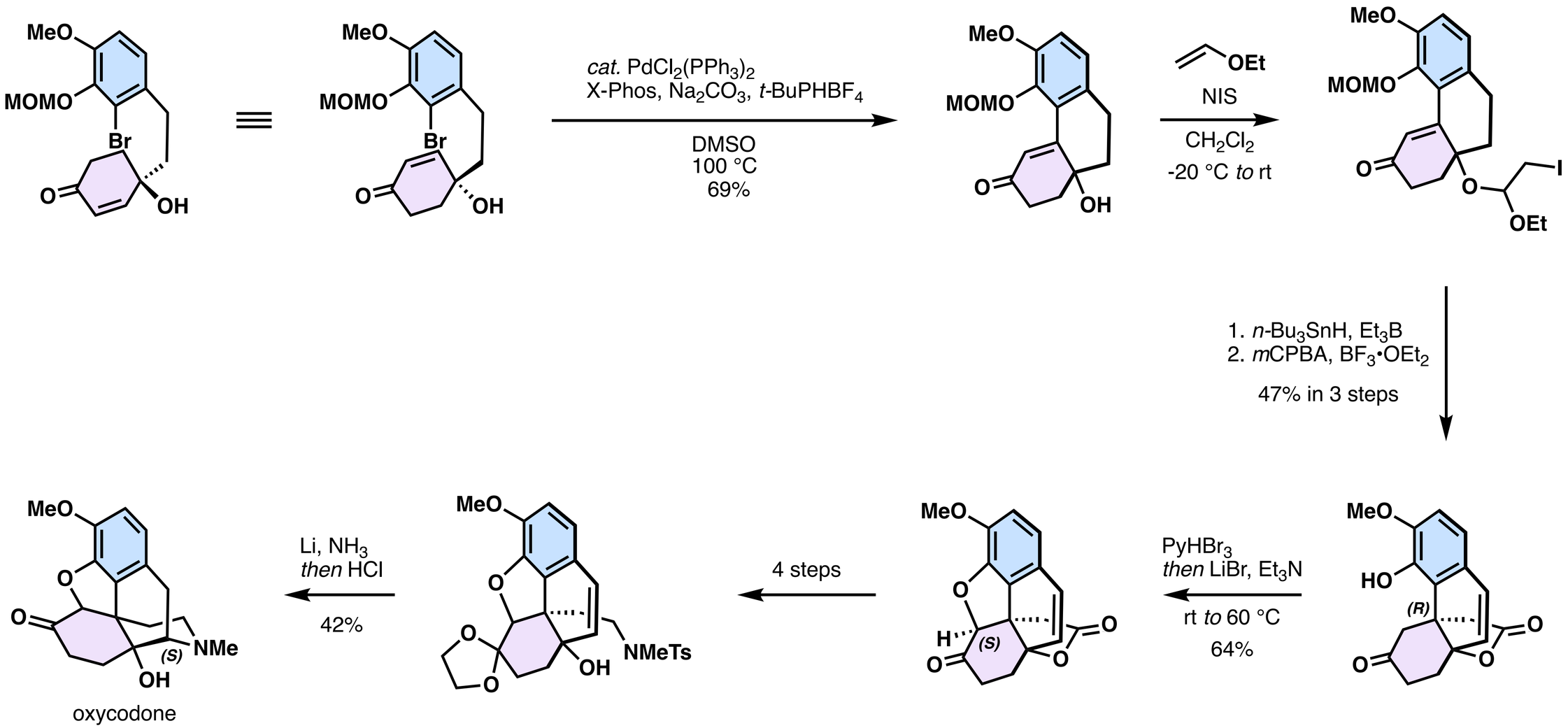
Park, K. H.; Chen, D. Y. K. *Chem. Commun.* **2018,** *54*, 13018–13021.

Oxycodone: Dienone Desymmetrization toward the Morphinan Framework



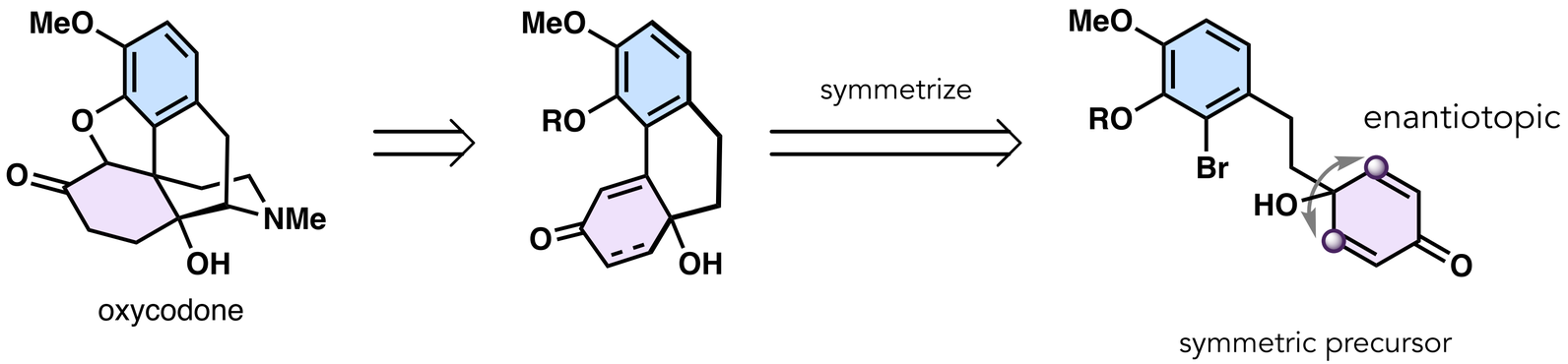
Park, K. H.; Chen, D. Y. K. *Chem. Commun.* **2018,** *54*, 13018–13021.

Oxycodone: Dienone Desymmetrization toward the Morphinan Framework



Park, K. H.; Chen, D. Y. K. *Chem. Commun.* **2018,** *54,* 13018–13021.

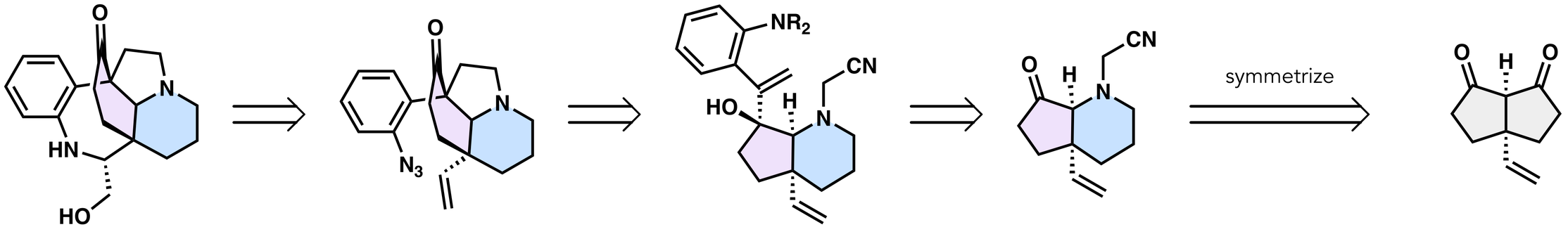
Oxycodone: Dienone Desymmetrization toward the Morphinan Framework



- Global desymmetrization established the core asymmetry of the molecule
- 2 new stereocenters were created during this key transformation
- The remaining stereocenters were introduced under internal stereochemical control

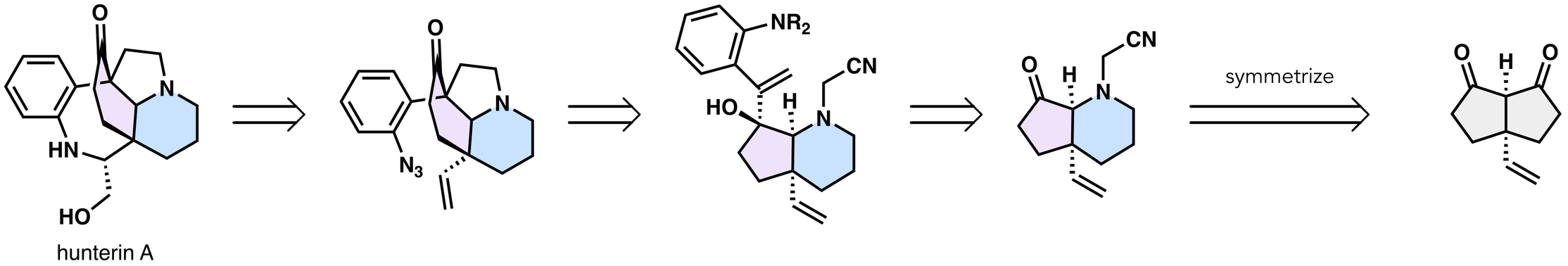
Park, K. H.; Chen, D. Y. K. *Chem. Commun.* **2018,** *54*, 13018–13021.

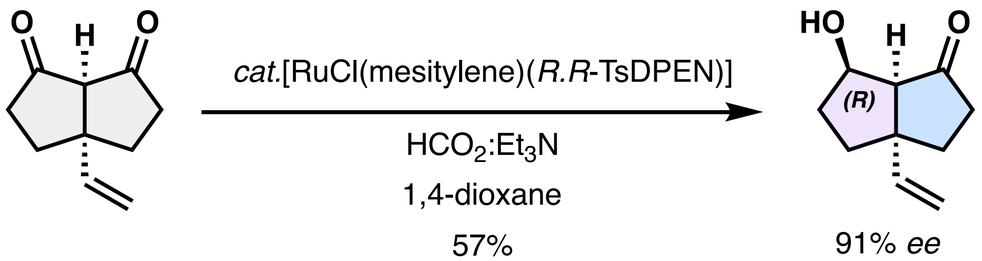
(–)-Hunterin A: Symmetry Breaking Followed by Divergent Skeletal Elaboration



Hicks, E. F.; Inoue, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2024,** *146*, 4340–4345.

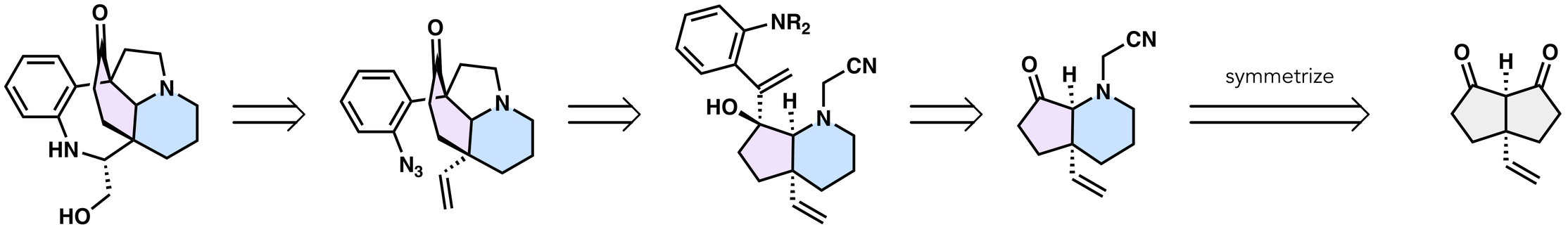
(–)-Hunterin A: Symmetry Breaking Followed by Divergent Skeletal Elaboration



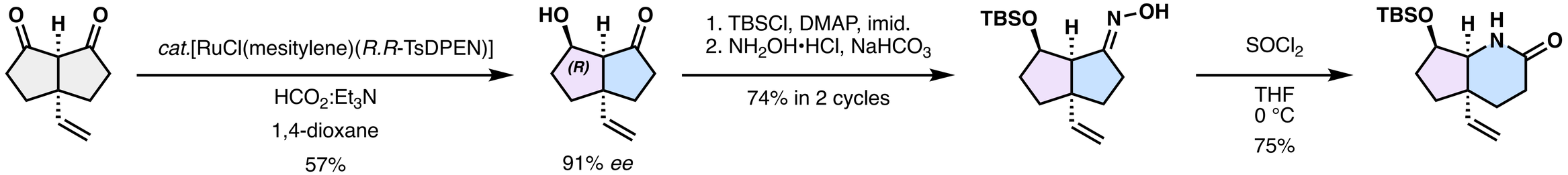


Hicks, E. F.; Inoue, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2024,** *146*, 4340–4345.

(–)-Hunterin A: Symmetry Breaking Followed by Divergent Skeletal Elaboration



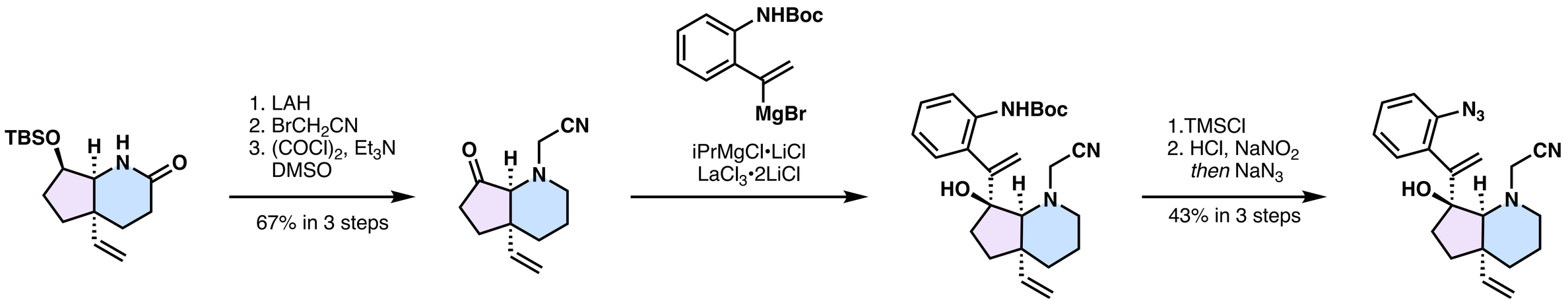
hunterin A



Beckmann rearrangment

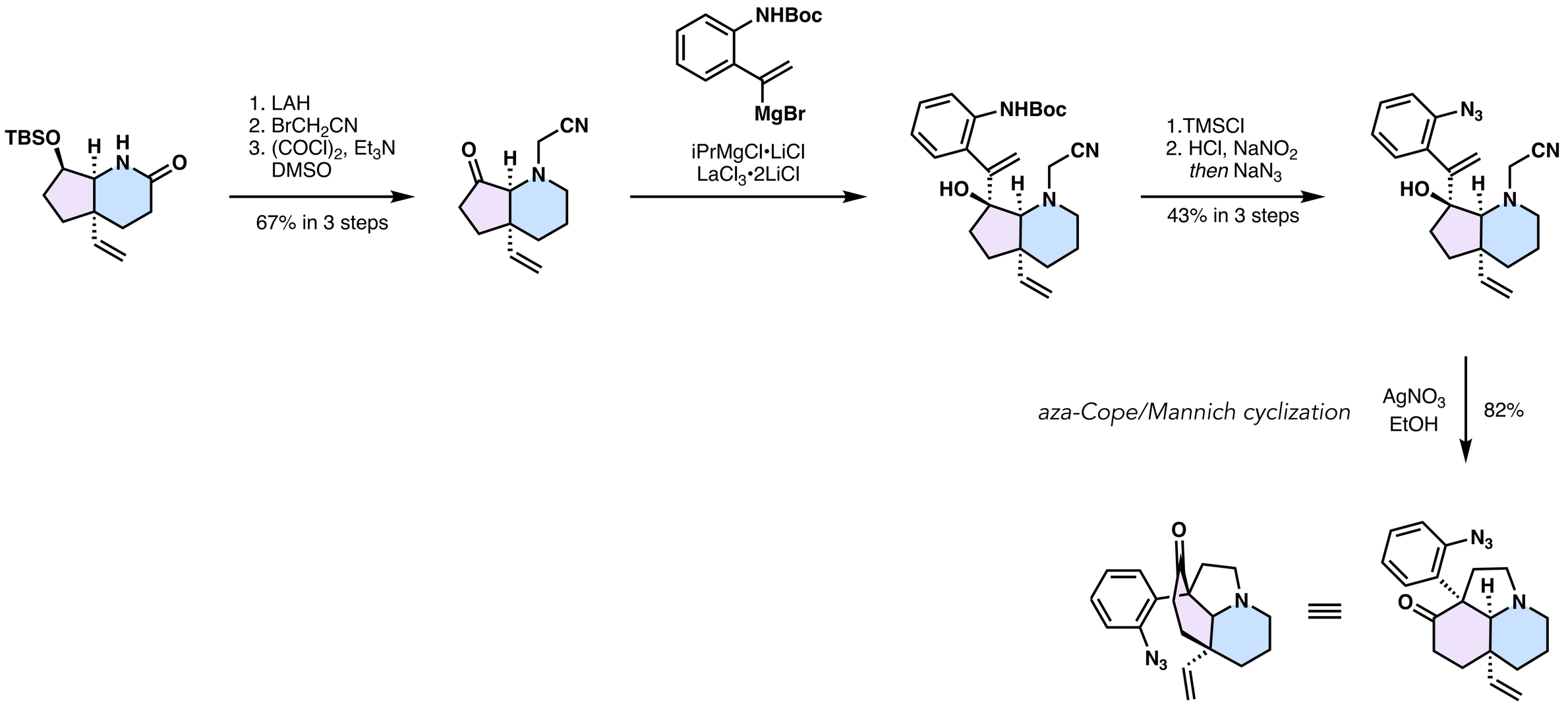
Hicks, E. F.; Inoue, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2024,** *146*, 4340–4345.

(–)-Hunterin A: Symmetry Breaking Followed by Divergent Skeletal Elaboration



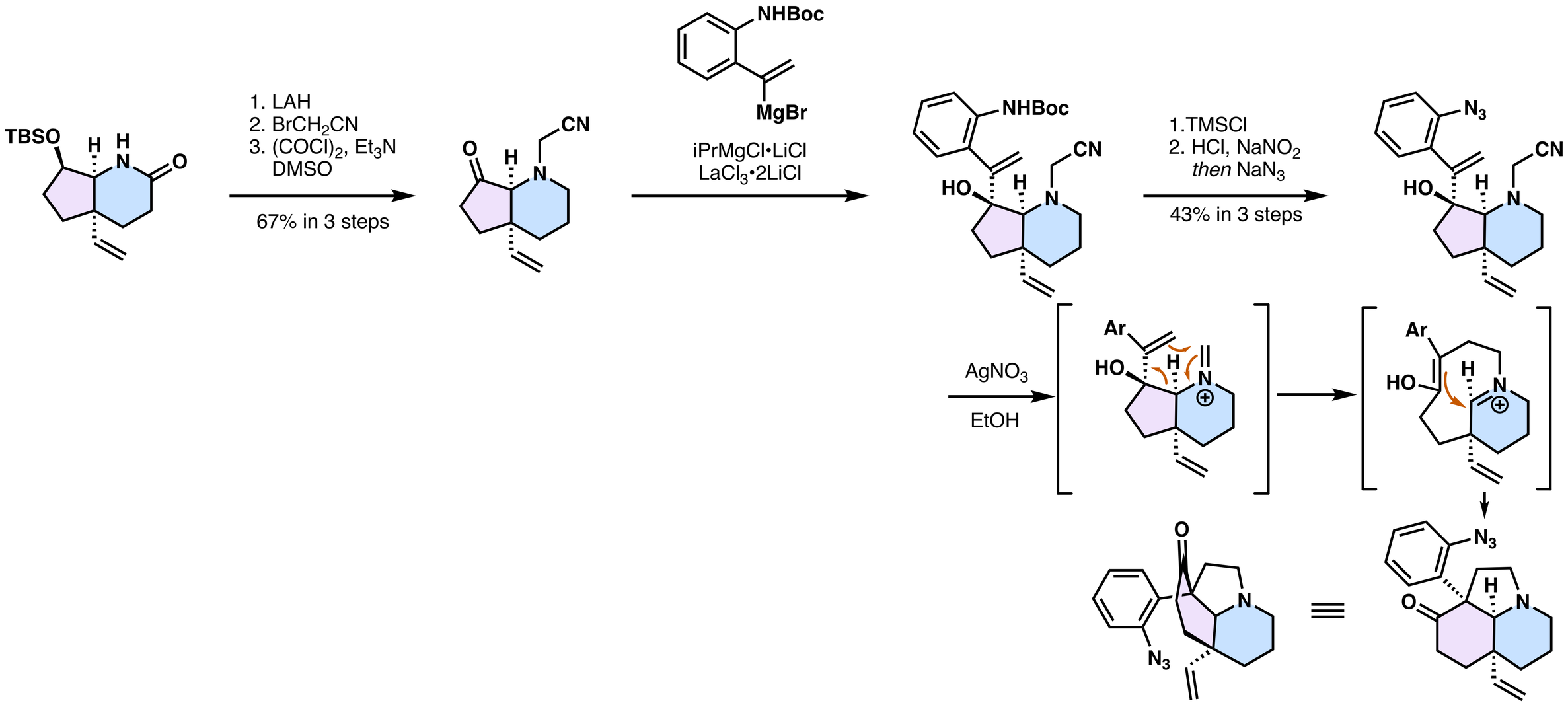
Hicks, E. F.; Inoue, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2024,** *146*, 4340–4345.

(–)-Hunterin A: Symmetry Breaking Followed by Divergent Skeletal Elaboration



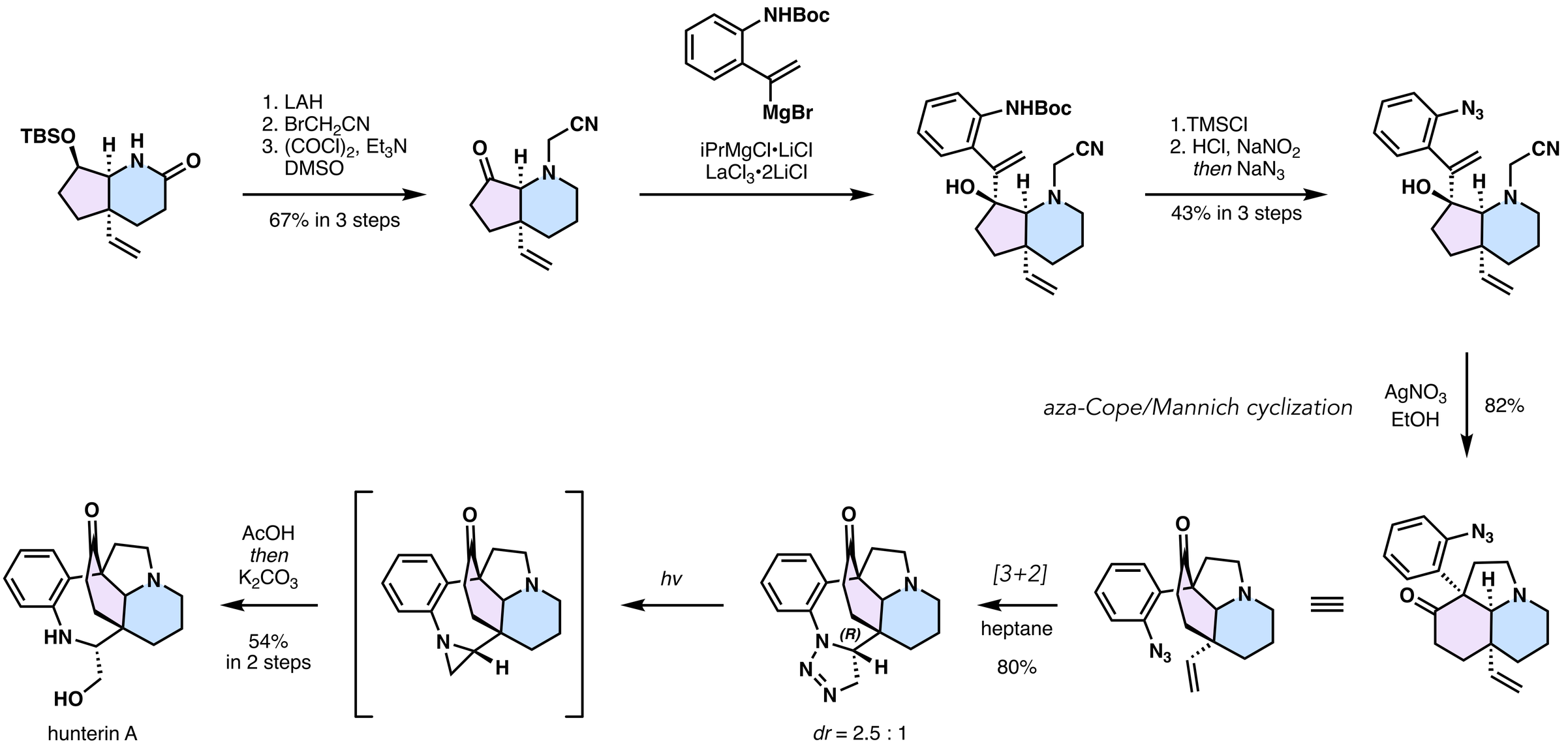
Hicks, E. F.; Inoue, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2024,** *146*, 4340–4345.

(–)-Hunterin A: Symmetry Breaking Followed by Divergent Skeletal Elaboration



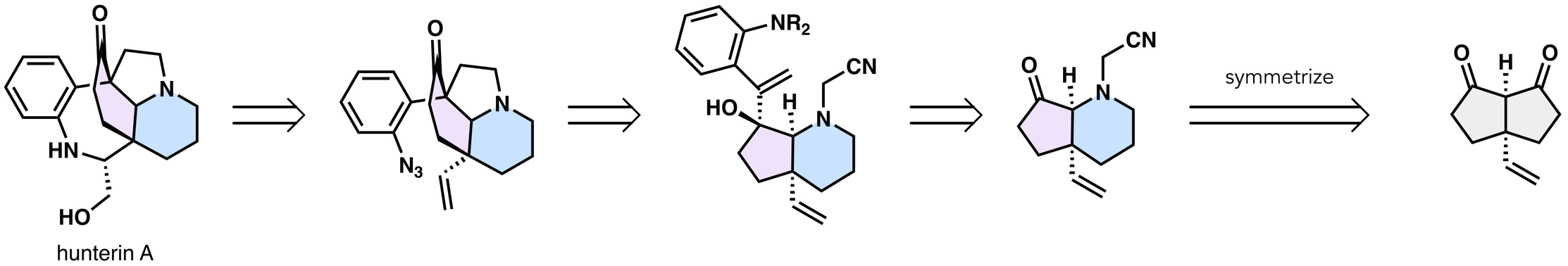
Hicks, E. F.; Inoue, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2024,** *146*, 4340–4345.

(–)-Hunterin A: Symmetry Breaking Followed by Divergent Skeletal Elaboration



Hicks, E. F.; Inoue, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2024,** *146*, 4340–4345.

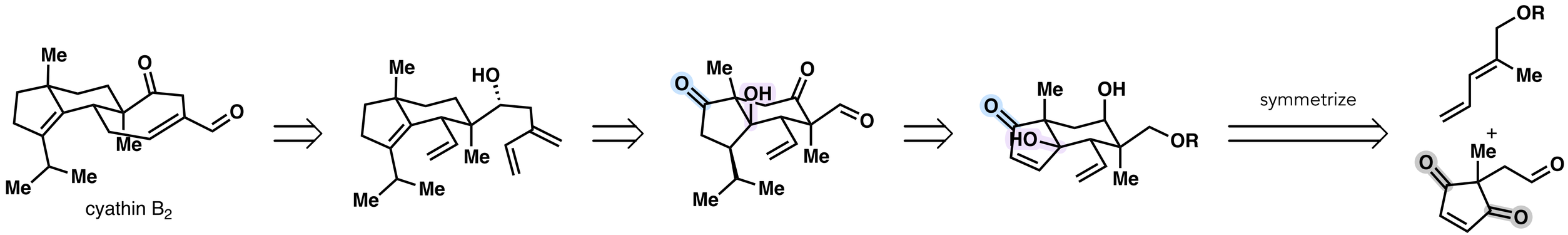
(–)-Hunterin A: Symmetry Breaking Followed by Divergent Skeletal Elaboration



- Desymmetrization creates a differentiated chiral intermediate
- One side proceeds through a Beckmann rearrangement
- The other side proceeds through an Overman aza-Cope–Mannich reaction
- Early symmetry breaking enables divergent construction of the alkaloid framework

Hicks, E. F.; Inoue, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2024,** *146*, 4340–4345.

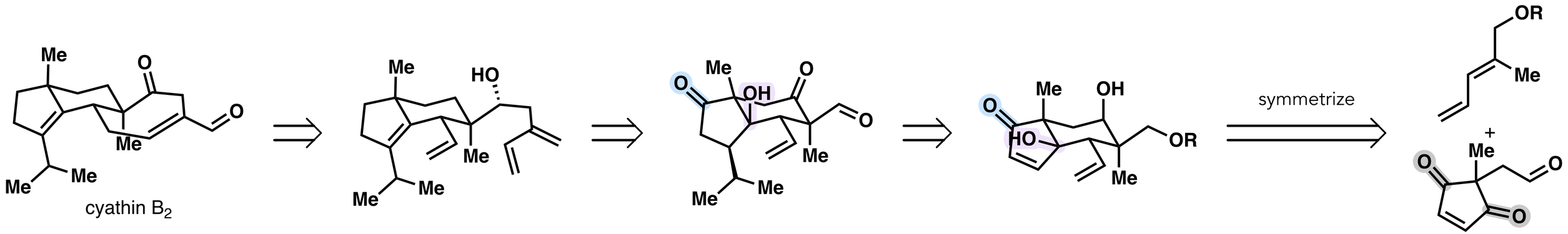
(–)-Cyathin B_2: One cascade, Five stereocenters

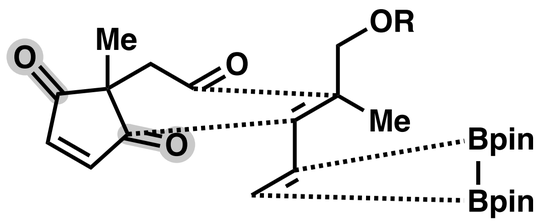


–

Wang, J.; Yin, J.; Li, Y.; *et al. J. Am. Chem. Soc.* **2024,** *146*, 25078–25087.

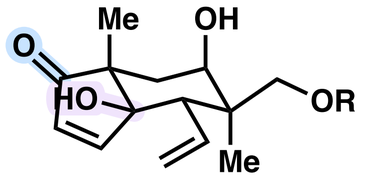
(–)-Cyathin B_2: One cascade, Five stereocenters





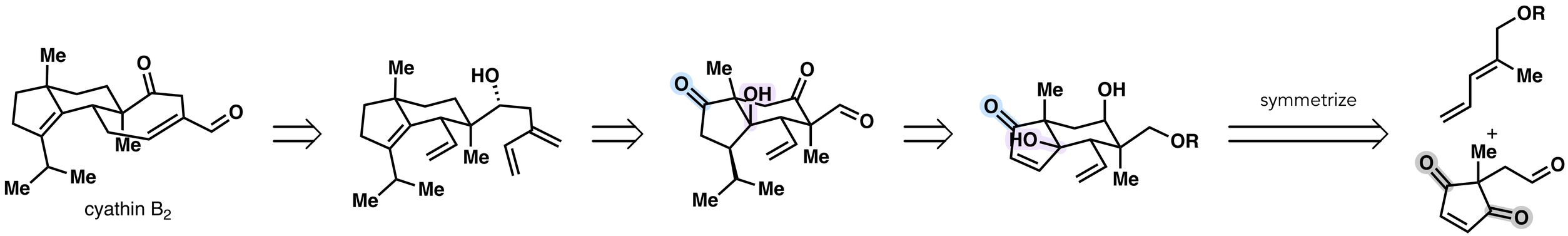
asymmetric diboration
&
desymmetric double allylboration

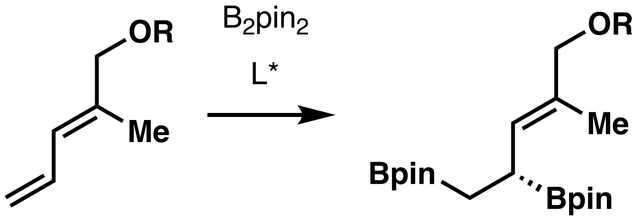
workup

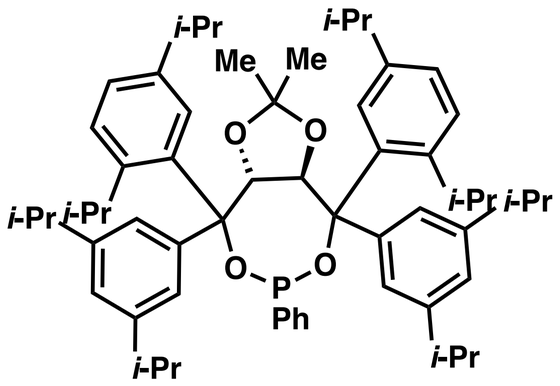


Wang, J.; Yin, J.; Li, Y.; *et al. J. Am. Chem. Soc.* **2024,** *146*, 25078–25087.

(–)-Cyathin B_2: One cascade, Five stereocenters



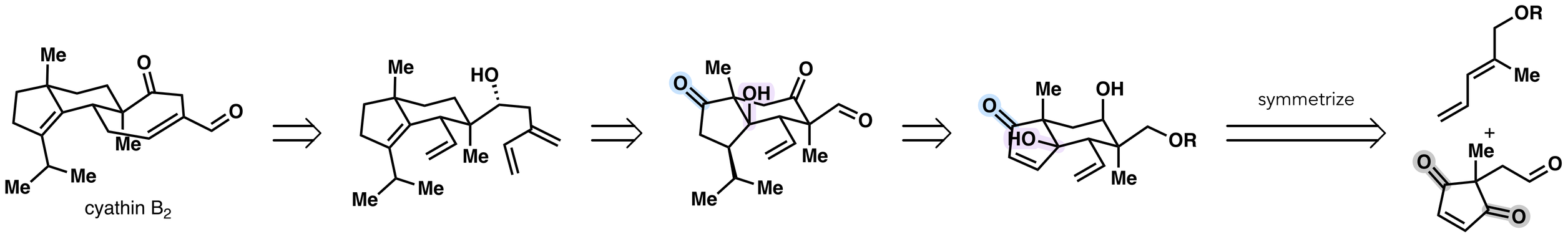


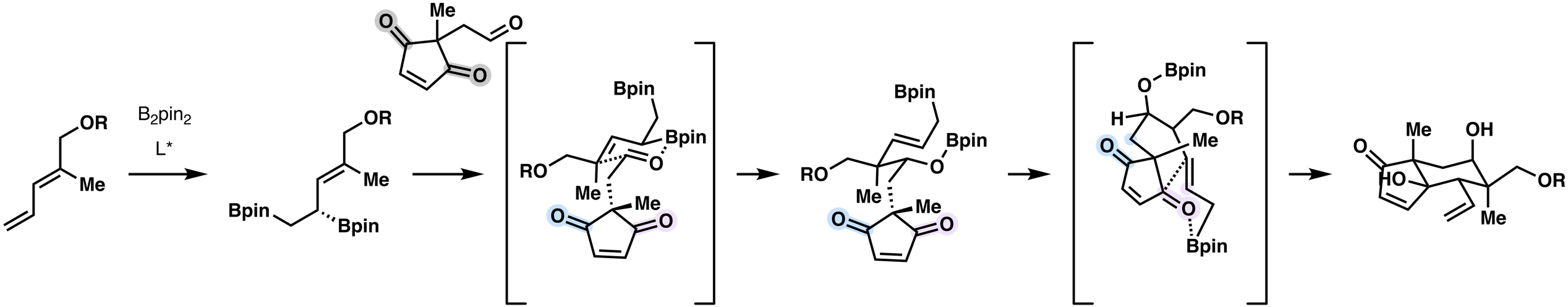


L*

Wang, J.; Yin, J.; Li, Y.; *et al. J. Am. Chem. Soc.* **2024,** *146*, 25078–25087.

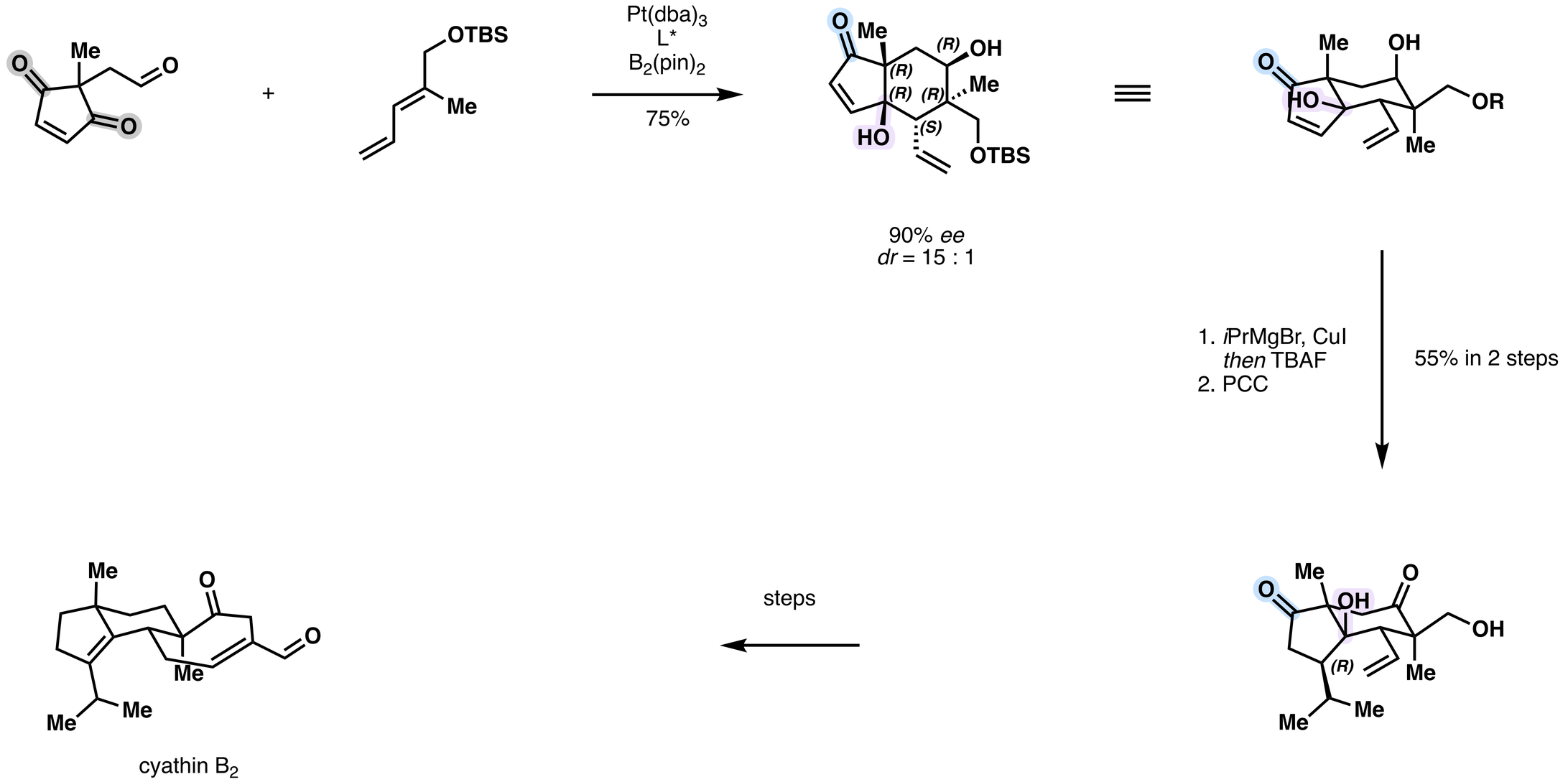
(–)-Cyathin B_2: One cascade, Five stereocenters





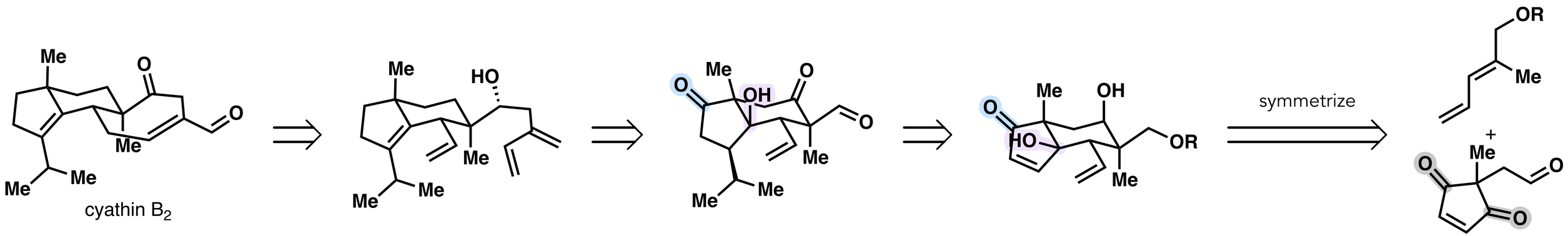
Wang, J.; Yin, J.; Li, Y.; *et al. J. Am. Chem. Soc.* **2024,** *146*, 25078–25087.

(–)-Cyathin B_2: One cascade, Five stereocenters



Wang, J.; Yin, J.; Li, Y.; *et al. J. Am. Chem. Soc.* **2024,** *146*, 25078–25087.

(–)-Cyathin B_2: One cascade, Five stereocenters

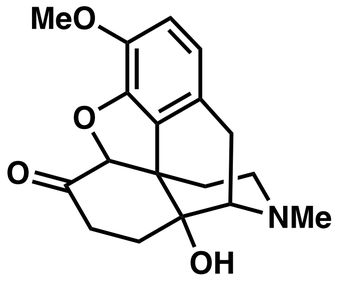


- A desymmetrizing cascade rapidly builds the bicyclic core
- The key step creates five new stereocenters in a single operation
- Among them, both quaternary stereocenters are established simultaneously
- Thus, symmetry breaking is directly translated into major stereochemical and skeletal complexity

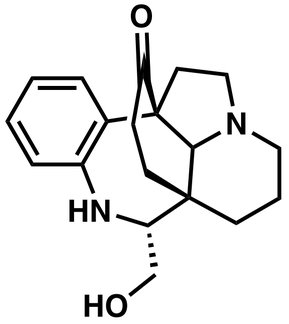
Wang, J.; Yin, J.; Li, Y.; *et al. J. Am. Chem. Soc.* **2024,** *146*, 25078–25087.

Overview

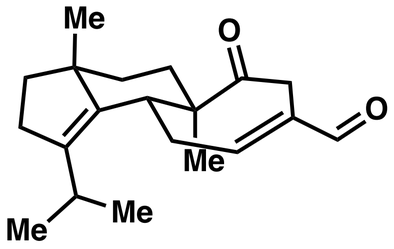
Global desymmetrization



oxycodone

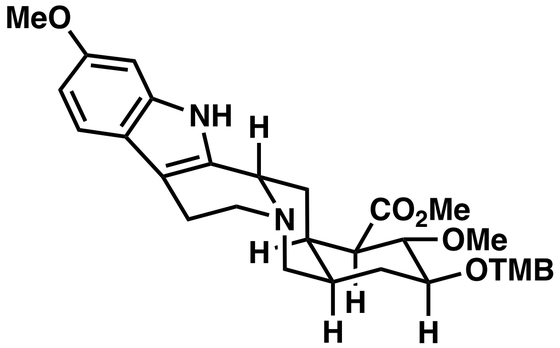


hunterin A

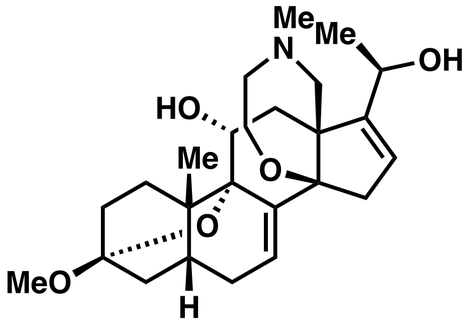


cyathin B_2

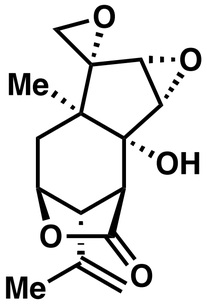
Local desymmetrization



reserpine

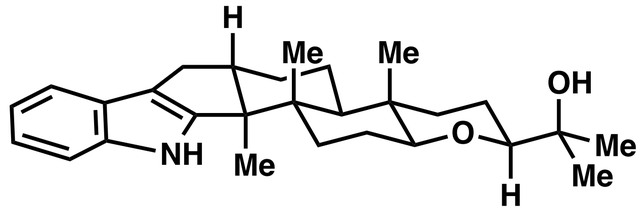


batrachotoxinin A

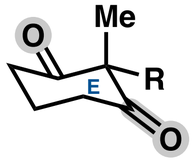


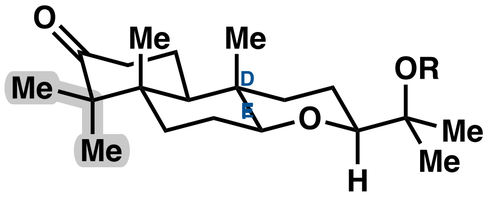
coriamyrtin

Combined global and local desymmetrization

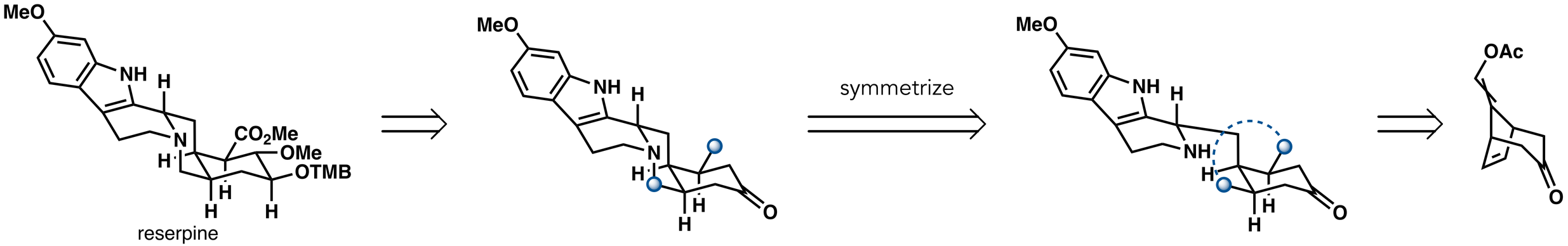


paspaline



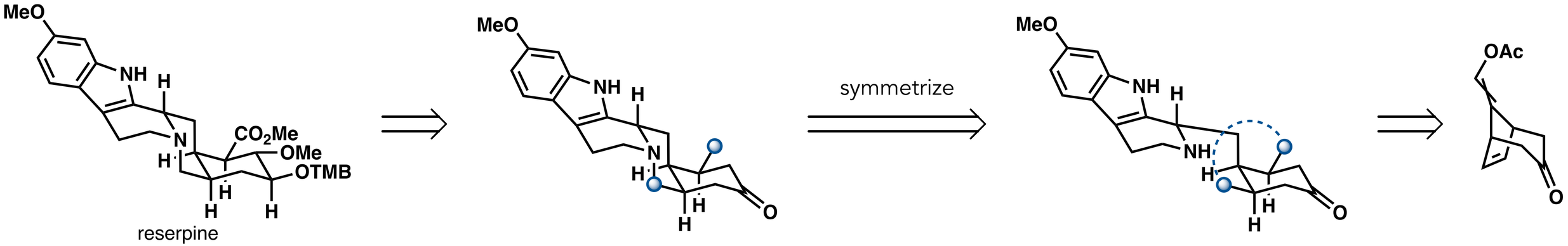


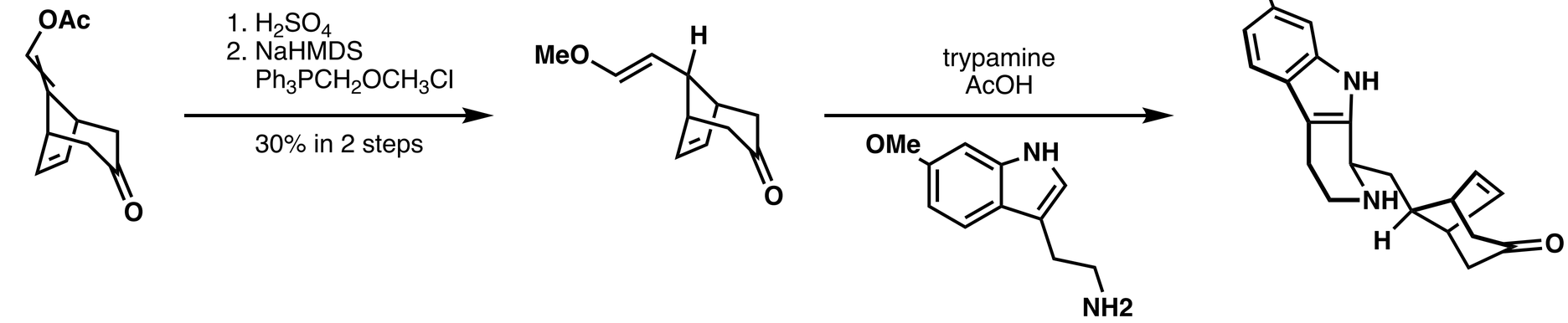
Reserpine: Internal Desymmetrization from a Nonstereogenic Precursor



Park, J.; Chen, D. Y. K. *Angew. Chem. Int. Ed.* **2018,** *57*, 16152–16156.

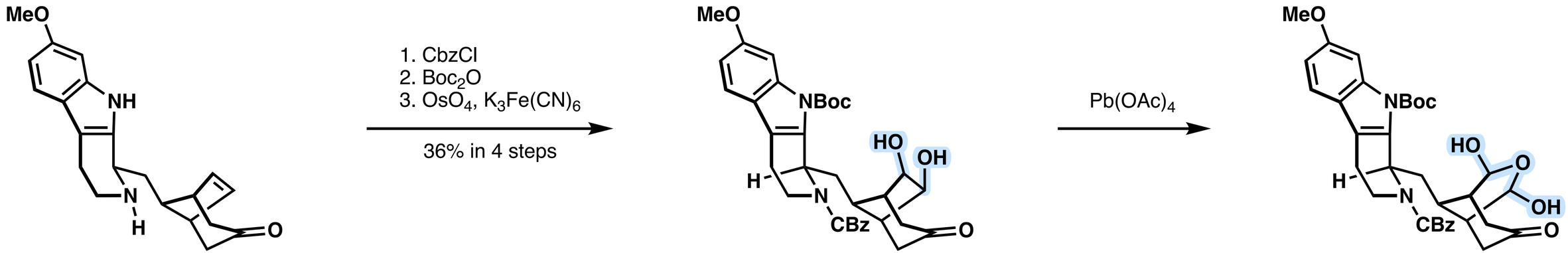
Reserpine: Internal Desymmetrization from a Nonstereogenic Precursor





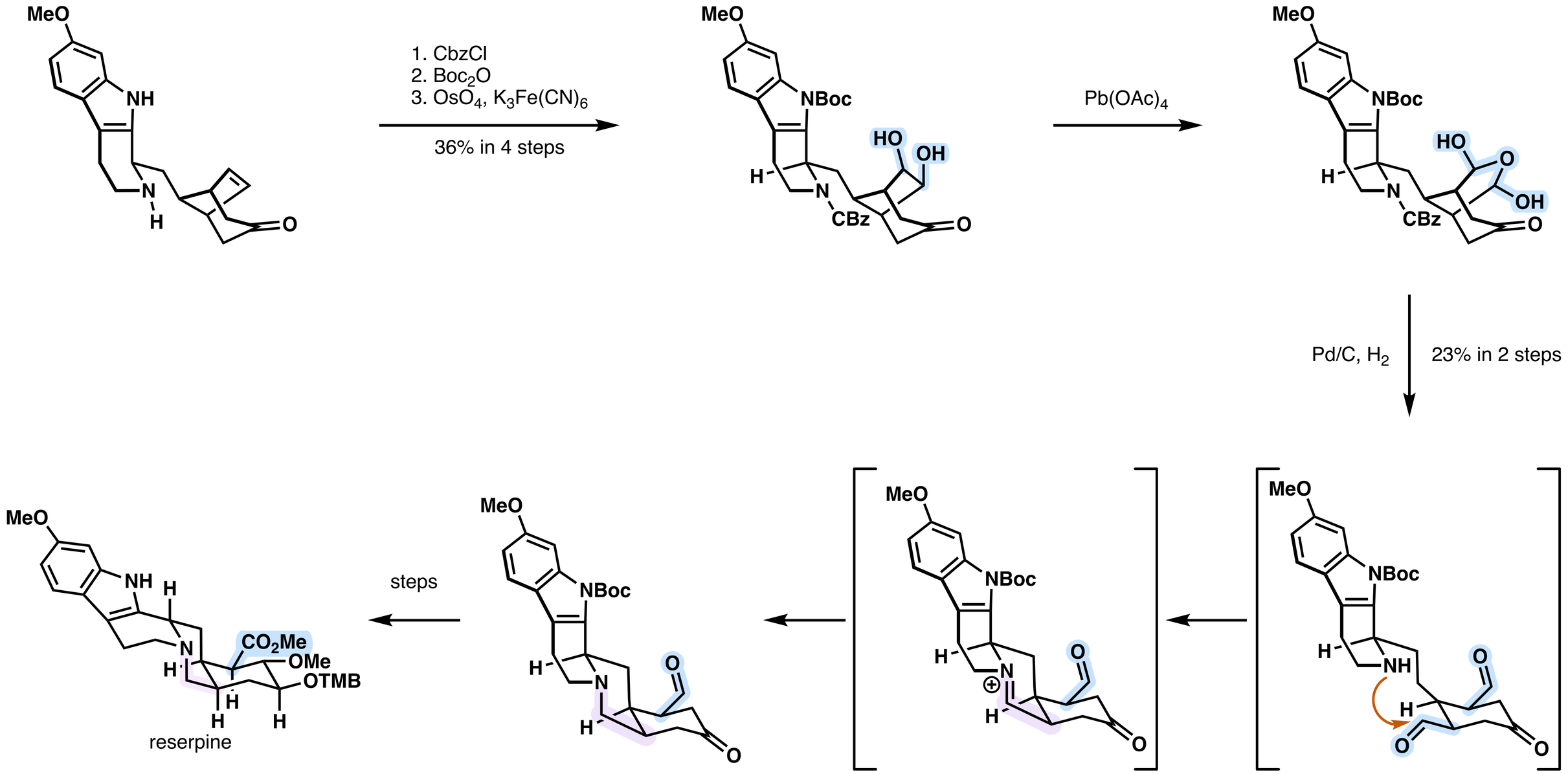
Park, J.; Chen, D. Y. K. *Angew. Chem. Int. Ed.* **2018,** *57*, 16152–16156.

Reserpine: Internal Desymmetrization from a Nonstereogenic Precursor



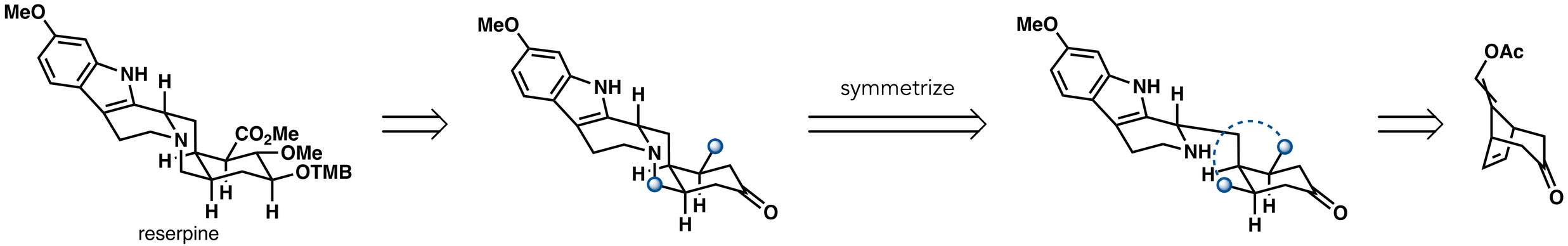
Park, J.; Chen, D. Y. K. *Angew. Chem. Int. Ed.* **2018,** *57*, 16152–16156.

Reserpine: Internal Desymmetrization from a Nonstereogenic Precursor



Park, J.; Chen, D. Y. K. *Angew. Chem. Int. Ed.* **2018,** *57*, 16152–16156.

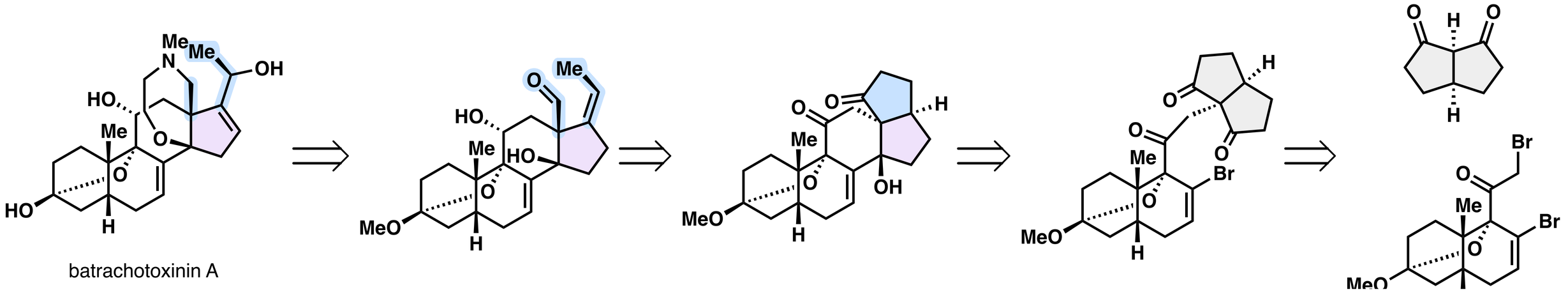
Reserpine: Internal Desymmetrization from a Nonstereogenic Precursor



- Internal desymmetrization replaces the need for stereodefined ring precursors
- A readily accessible, nonstereogenic precursor can be used instead
- This simplifies the route and introduces chirality in a later strategic step

Park, J.; Chen, D. Y. K. *Angew. Chem. Int. Ed.* **2018,** *57*, 16152–16156.

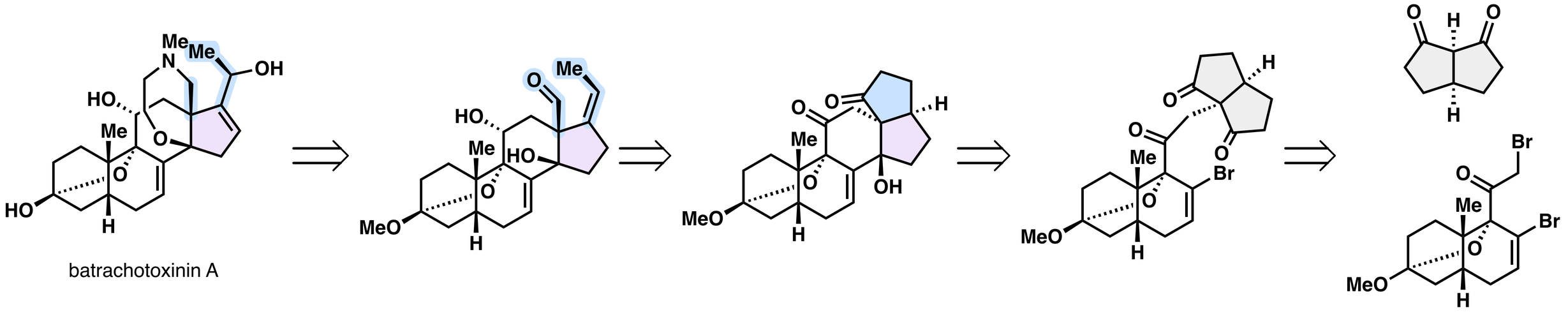
(–)-Batrachotoxinin A: A Local Desymmetrizing Cyclization to the Hexacyclic Core

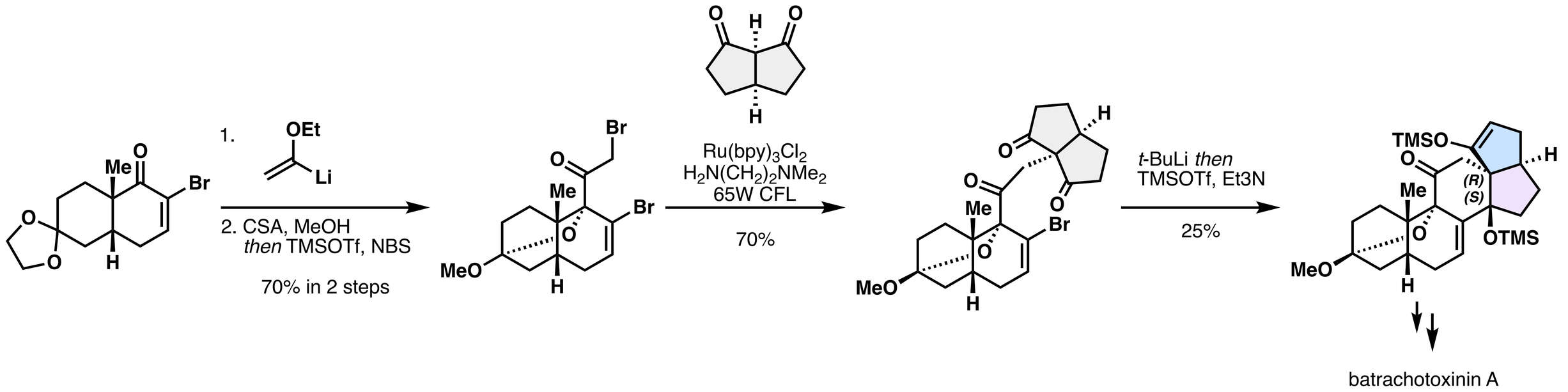


batrachotoxinin A

Guo, Y.; Guo, Z.; Luo, T.; *et al. J. Am. Chem. Soc.* **2020,** *142*, 3675–3679.

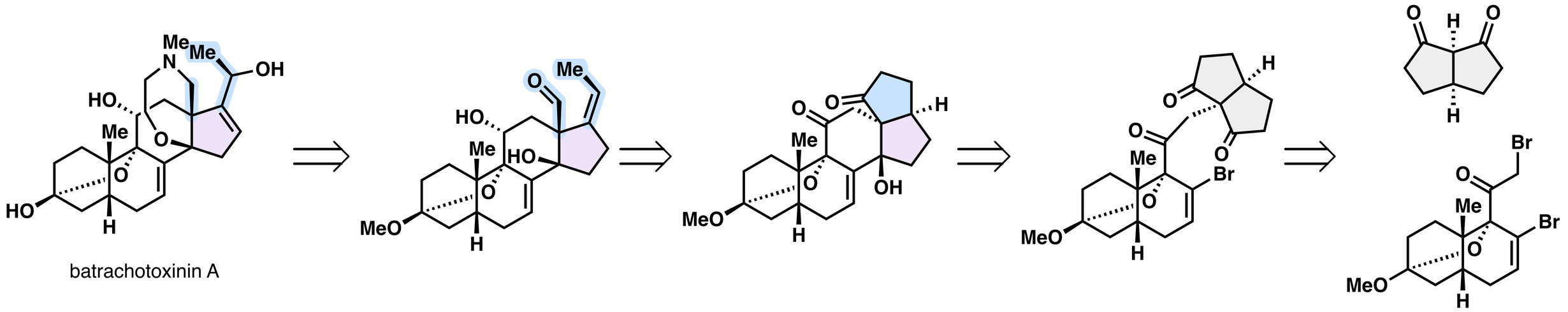
(–)-Batrachotoxinin A: A Local Desymmetrizing Cyclization to the Hexacyclic Core





Guo, Y.; Guo, Z.; Luo, T.; *et al. J. Am. Chem. Soc.* **2020,** *142*, 3675–3679.

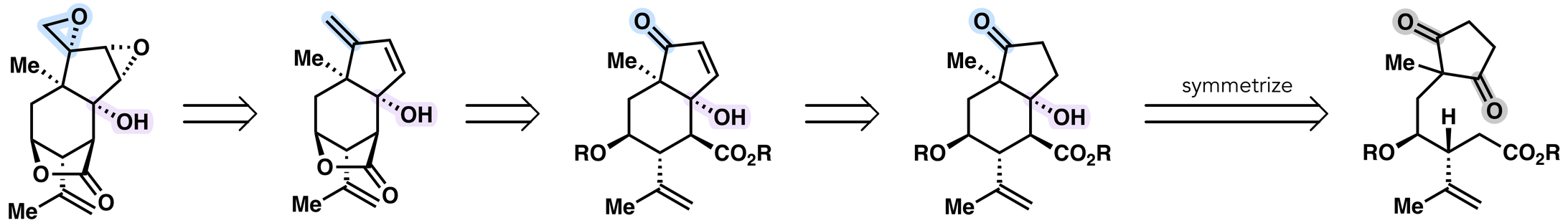
(–)-Batrachotoxinin A: A Local Desymmetrizing Cyclization to the Hexacyclic Core



- A local desymmetrizing cyclization rapidly builds the hexacyclic core
- Existing stereochemical information is used to control further stereochemical differentiation
- This gives a stereochemically economical route to batrachotoxinin A

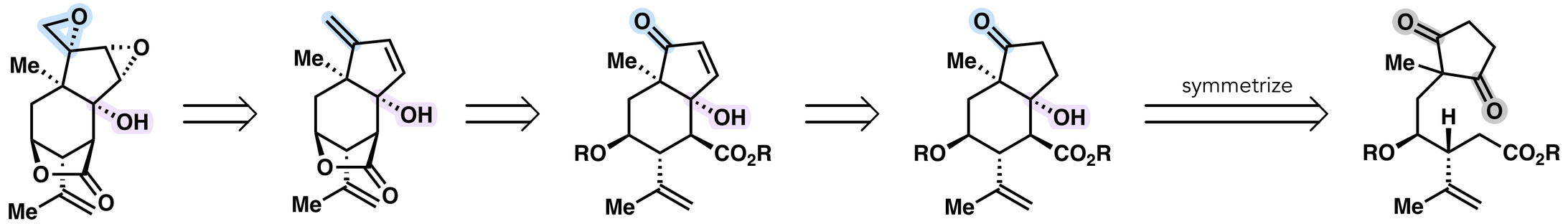
Guo, Y.; Guo, Z.; Luo, T.; *et al. J. Am. Chem. Soc.* **2020,** *142*, 3675–3679.

(+)-Coriamyrtin: A Desymmetrizing Aldol Strategy to the cis-Hydrindane Core

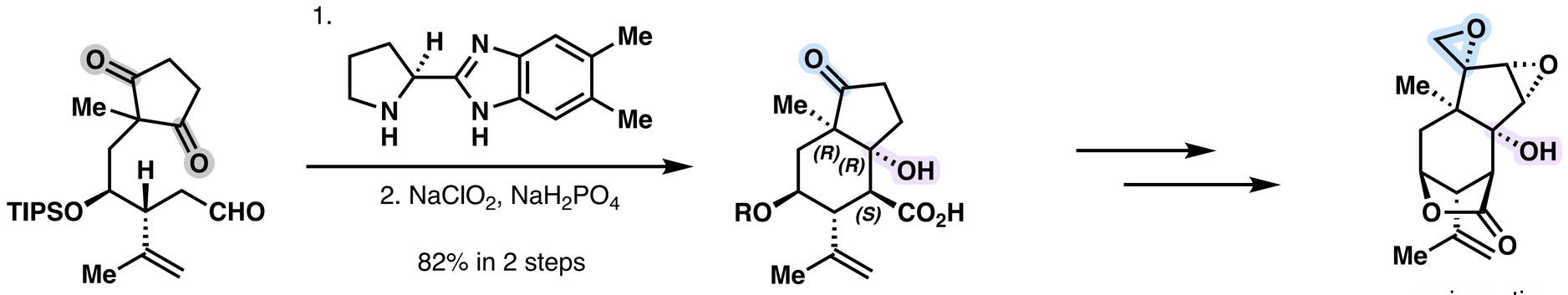


Ikeuchi, K.; Haraguchi, S.; Tanino, K.; *et al. Org. Lett.* **2023,** *25*, 1874–1878.

(+)-Coriamyrtin: A Desymmetrizing Aldol Strategy to the cis-Hydrindane Core



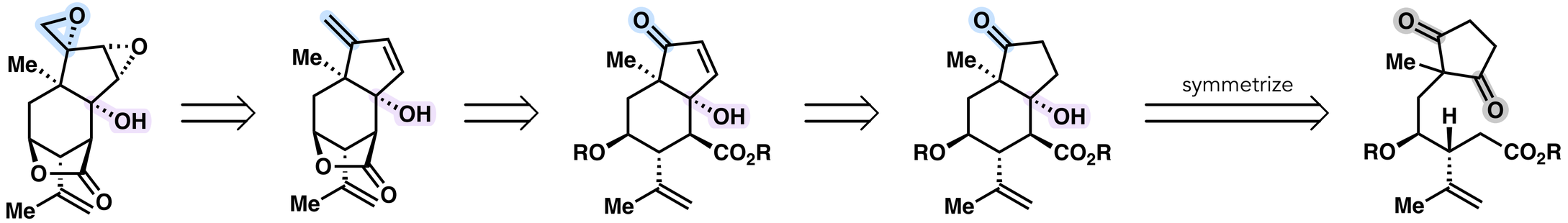
coriamyrtin



coriamyrtin

Ikeuchi, K.; Haraguchi, S.; Tanino, K.; *et al. Org. Lett.* **2023,** *25*, 1874–1878.

(+)-Coriamyrtin: A Desymmetrizing Aldol Strategy to the cis-Hydrindane Core

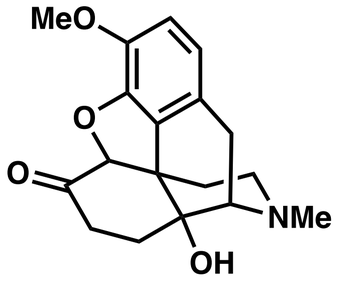


- Desymmetrizing intramolecular aldol reaction
- Efficient construction of the cis-hydrindane core
- Enables late-stage installation of the 1,3-diepoxide motif

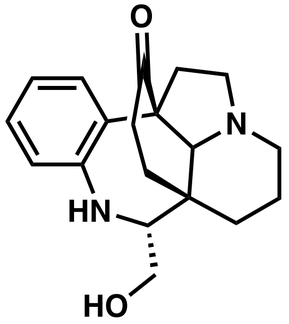
Ikeuchi, K.; Haraguchi, S.; Tanino, K.; *et al. Org. Lett.* **2023,** *25*, 1874–1878.

Overview

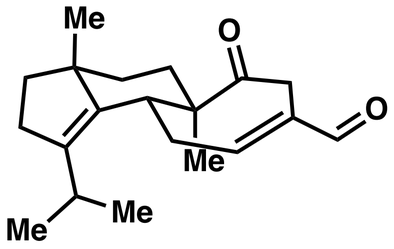
Global desymmetrization



oxycodone

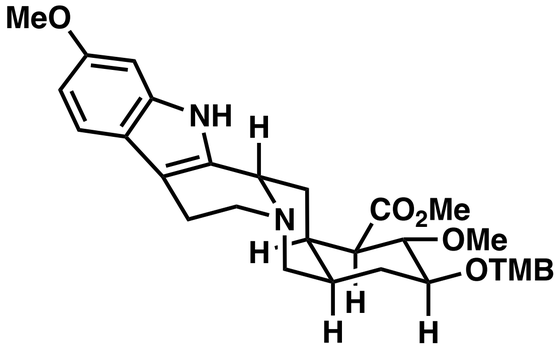


hunterin A

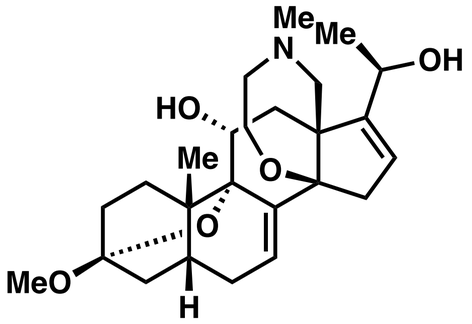


cyathin B_2

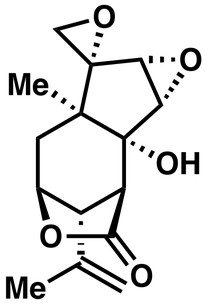
Local desymmetrization



reserpine

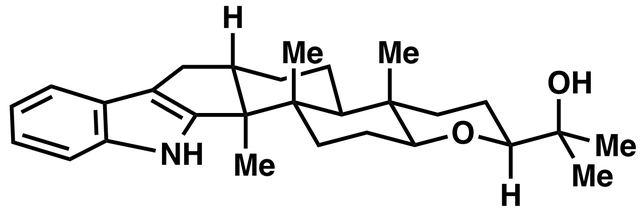


batrachotoxinin A

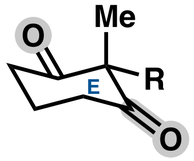


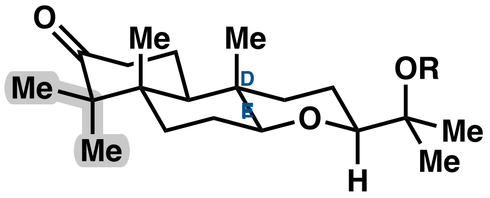
coriamyrtin

Combined global and local desymmetrization

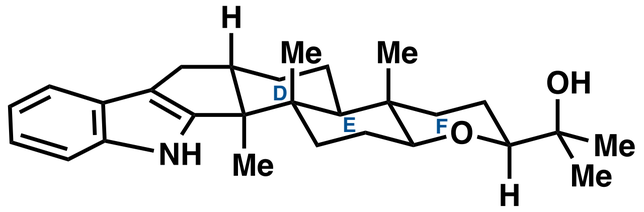


paspaline

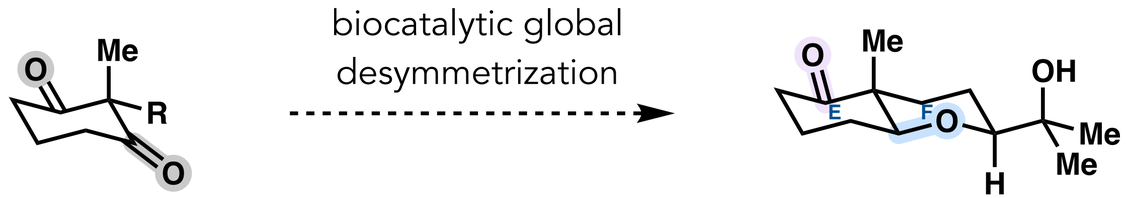


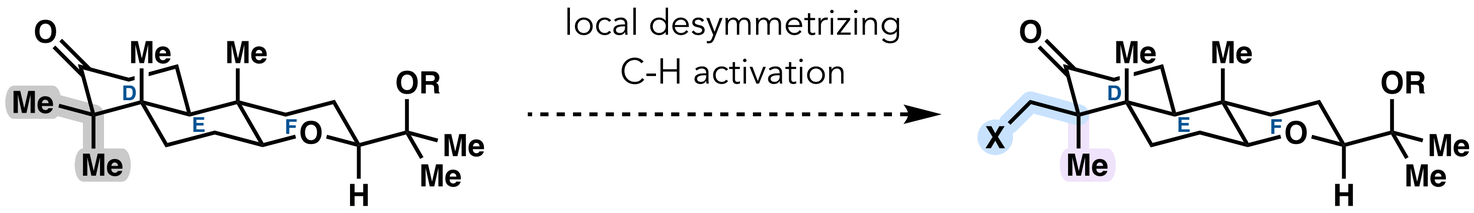


Paspaline: Desymmetrization at Multiple Stages of Route Design



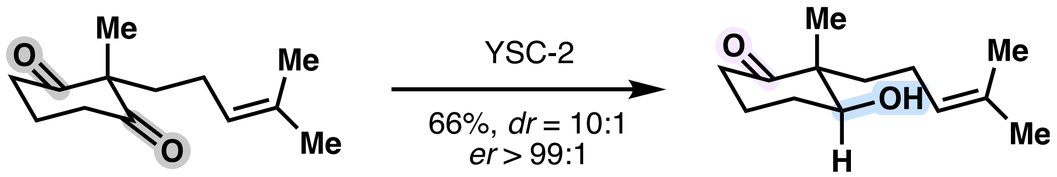
paspaline





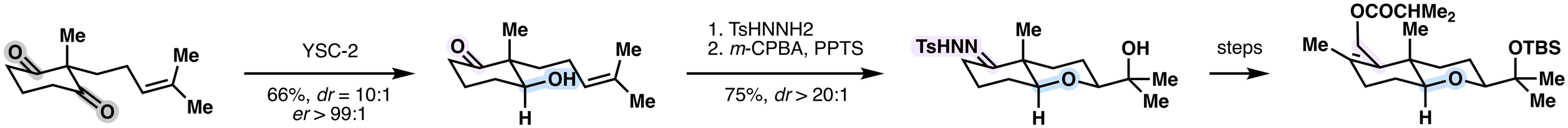
Sharpe, R. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2015,** *137*, 4968–4971.

Paspaline: Desymmetrization at Multiple Stages of Route Design



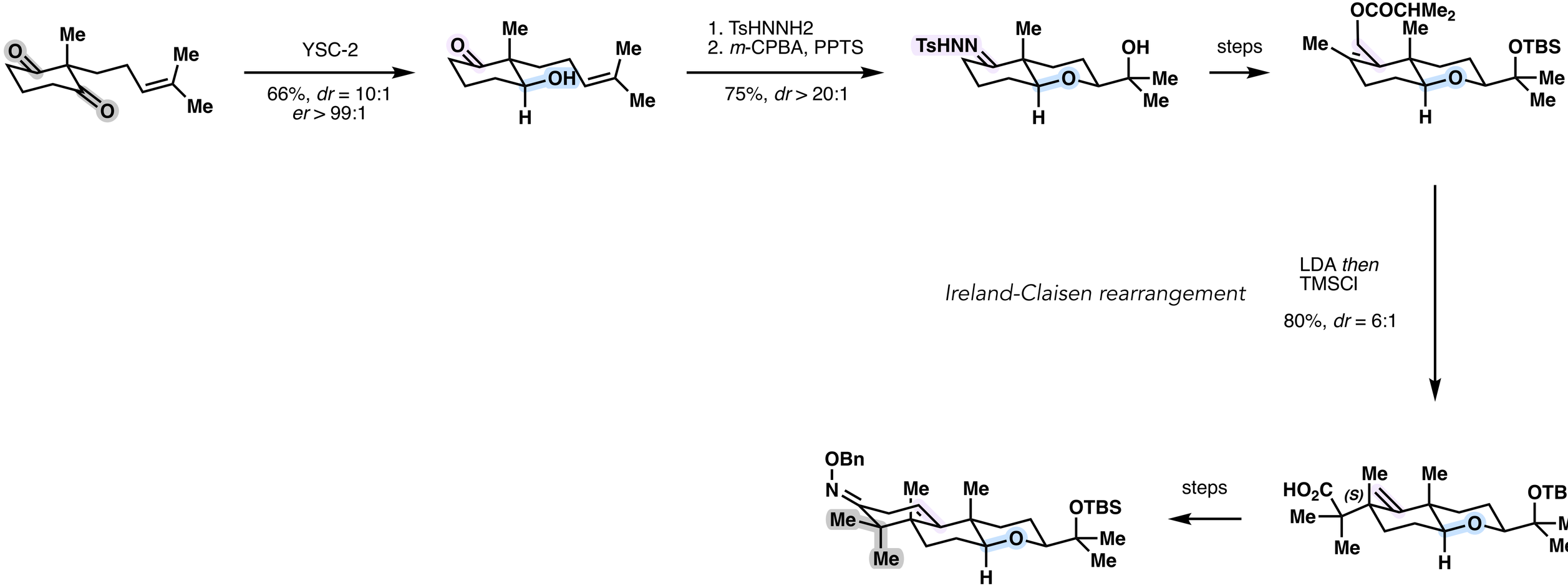
Sharpe, R. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2015,** *137*, 4968–4971.

Paspaline: Desymmetrization at Multiple Stages of Route Design



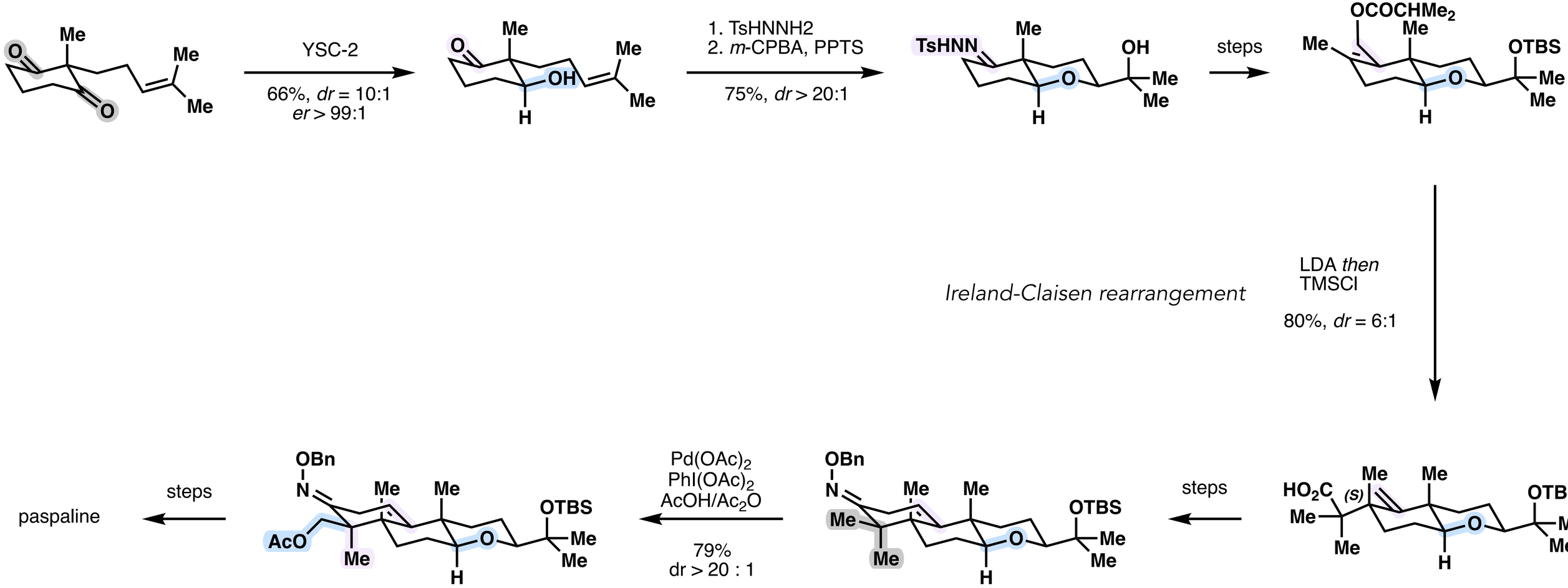
Sharpe, R. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2015,** *137*, 4968–4971.

Paspaline: Desymmetrization at Multiple Stages of Route Design



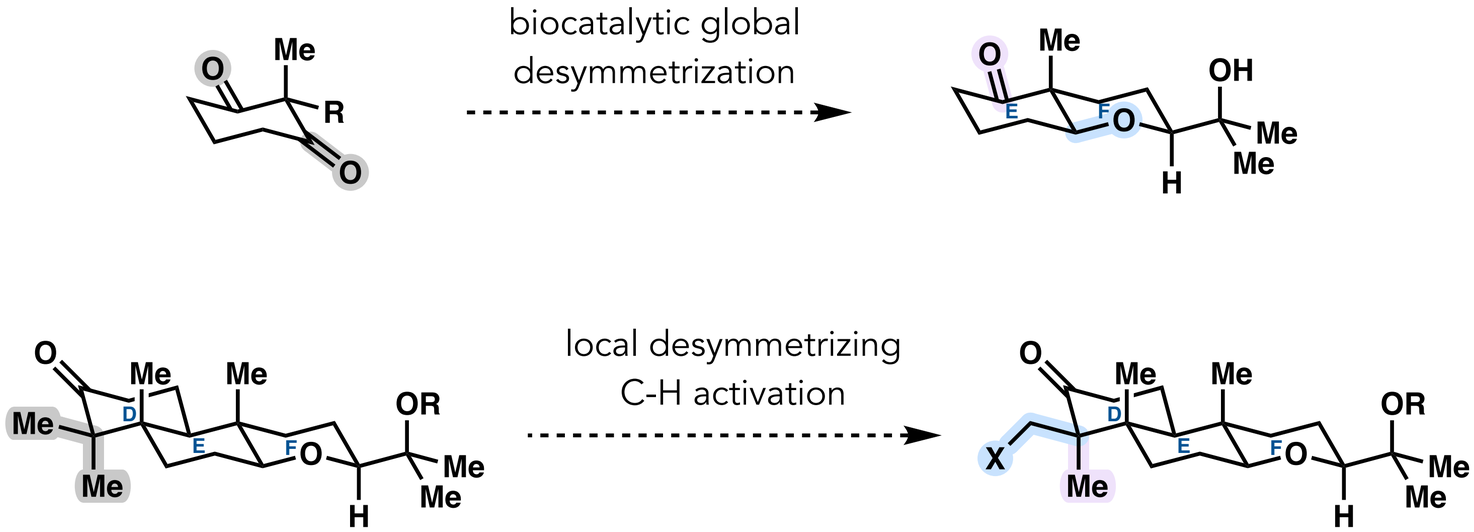
Sharpe, R. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2015,** *137*, 4968–4971.

Paspaline: Desymmetrization at Multiple Stages of Route Design



Sharpe, R. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2015,** *137*, 4968–4971.

Paspaline: Desymmetrization at Multiple Stages of Route Design



- Both global and local desymmetrization are used in one synthesis
- Global desymmetrization sets the early stereochemical framework
- Local desymmetrization installs a difficult late-stage quaternary center
- Desymmetrization acts as a route-design strategy, not just a single reaction

Sharpe, R. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2015,** *137*, 4968–4971.

Outlook

- Symmetry can be a strategic opportunity in synthesis
- Desymmetrization converts simple symmetric precursors into complex chiral molecules
- By separating scaffold assembly from stereochemical installation, it has become a valuable design strategy in modern total synthesis
- However, its success largely depends on identifying suitable hidden symmetry

Liu, H.; Tang, K.; Jia, Y.; *et al. Chem. Soc. Rev.* **2025,** *54*, 6208–6237.