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Organic Chemistry in Action

Workbook of Modern Literature Examples

Horace Luong

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Workbook of Modern Literature Examples

Edition 1.0

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Acknowledgements

Land Acknowledgement

The writing of this book took place at the University of Manitoba, on the traditional lands of the Anishinaabeg, Ininiwak, Anisininewuk, Dakota Oyate, Dene, and Inuit peoples, and on the National Homeland of the Red River Métis. I acknowledge this with gratitude and respect, while recognizing the harms and inequities that have affected Indigenous communities. I remain committed to learning from the past and contributing to a more just and inclusive future.

Manifold Adaptation Team

I am grateful to Glenn Bergen and Nicholas Lysecki of University of Manitoba Libraries for their expertise and support in publishing this book as an OER. Their assistance with formatting, organization, accessibility, and technical implementation was invaluable in bringing this project to completion.

Microsoft Copilot

I acknowledge using Microsoft Copilot as a writing and editorial assistance tool during the preparation of this workbook. Copilot was used to support drafting, editing, and refinement of selected text.

Introduction

Why this book?

I have been teaching organic chemistry for over two decades and I often hear learners asking, "When am I ever going to use this?" So I wrote this workbook because I wanted learners to practice the skills that matter most in introductory organic chemistry: drawing reaction mechanisms, retro synthesis analysis and predicting reaction outcomes (the classic "box-type questions") while seeing, concretely, that this material lives outside the classroom. Every problem here is built from a real reaction pulled from the research literature. That said, finding recent examples of material that is typically taught in introductory organic chemistry courses wasn't always possible. Chemistry moves fast, and some of the transformations we still teach have been superseded by better methods in modern labs.

To learn organic chemistry, it involves recognizing patterns and not so much memorizing. A core topic in organic chemistry is learning reaction mechanisms for various reactions. It's common for learners to be overwhelmed by all the reactions they have to "memorize" however if learners learn the basics and then apply that to what they encounter, it's much more manageable.

Organization of the workbook

This workbook is organized by topic rather than by course sequence. Although most introductory organic chemistry courses cover similar reactions, the order of presentation varies. After surveying numerous textbooks and course syllabi, I divided the material into self-contained reaction units that instructors can assign to students. The workbook assumes learners have already encountered the foundational concepts in lecture relevant to the sections.

This is a living project, and I know it isn't perfect. If you spot an error or have examples you think would be helpful to include, I'd genuinely like to hear from you! Here's the link to the feedback form for additions, errors and suggestions: Feedback Form for Organic Chemistry in Action

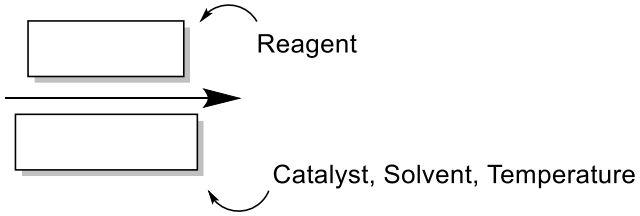
Message to the learner

To learn organic chemistry, you need to do problems as opposed to "study". So this workbook is a way to facilitate that problems aspect, and showing what you're learning has real applications. The molecules in these problems will look intimidating at first since they're drawn from real papers, so they may come heavily decorated with functional groups or larger structures. Please don't panic and focus on looking past the decoration, find the functional group you *do* recognize, and start there. That skill of ignoring the noise to see the reactive core is half of what organic chemistry is. Bigger picture, in life, you want to be able to see the signals and ignore the noise to maximize your efficiency, decrease stress and make good decisions, so treat organic chemistry as a way to start training that essential skill.

A few practical notes on using this workbook:

1. You'll find three kinds of questions: box-type questions (fill in the missing reactant, reagent, or product), mechanism problems, and multistep syntheses that ask you to string several transformations together or predict the product based on several transformations to a reactant. Each of these types of questions trains learners in different aspects:

Box-type questions: having the learners fill in a missing reactant, reagent (including solvents and temperature (if necessary to mention)), or product trains a learner to recognize and recall reactions from their vocabulary. For standard convention, boxes like this represent:



For reactions where the product is drawn, aim for the most stable product unless otherwise indicated (in the hint or temperature conditions suggests otherwise). Don't let the size of the boxes mislead you. They vary randomly in size on purpose.

Reaction mechanisms questions: having the learners draw the arrow pushing mechanism trains the learner on causal reasoning (being able to explain how a reaction occurs to get from a reactant to a product and why a particular product(s) would be made).

Multistep/Retrosynthesis questions: asking the learner to draw appropriate transformations from a vocabulary of reactions to get to a product trains learners to plan strategically

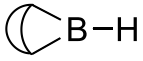
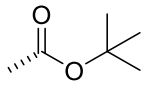
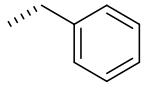
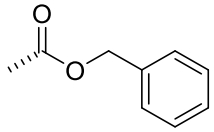
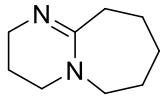
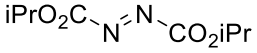
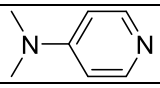
2. Within each section, the problems are arranged randomly for relevant content and difficulty, the randomness reflects what happens in real life.
3. The solutions manual is freely available however it only has answers to the box-type questions and multi-step questions since one can look those up anyway in the literature. The mechanism answers are not provided to encourage learners to work through their answers and then to compare with others and/or discuss with their instructor. That said, some of the journal articles will present a mechanism. Please note that the

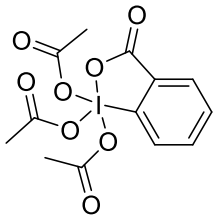
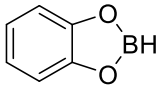
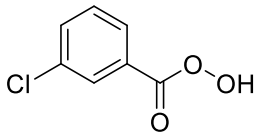
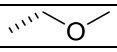
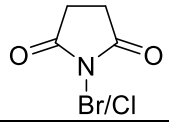
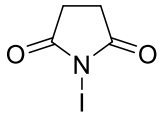
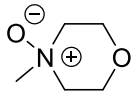
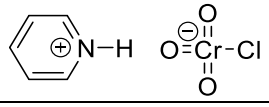
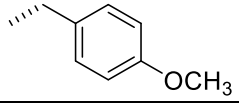
answers I give are what the literature reports. In organic chemistry, there's sometimes more than one defensible answer. If yours differs from mine, talk about it with your instructor.

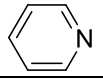
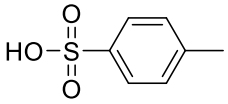
Message to the instructor

Please look through the problems before assigning them since not every reaction here may match what your course covers. Feel free to use the whole book for your course or even adapt portions of it for your assessments. My intention in writing this book is to provide a resource to help make the teaching easier whilst providing relevance for learners.

Abbreviations

Ac	Acetyl	$-COCH_3$
Am	Pentyl	$-CH_2CH_2CH_2CH_2CH_3$
Ar	Aryl	
9-BBN	9-Borabicyclo[3.3.1]nonane	 You can abbreviate the structure of 9-BBN as  in your reaction mechanisms.
Boc	Tert-butyloxycarbonyl	
Bz	Benzyl	
Bu	Butyl	$-CH_2CH_2CH_2CH_3$
Cbz	Benzyloxycarbonyl	
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	 Used as a large, bulky base.
DCE	1,2-Dichloroethane	$ClCH_2CH_2Cl$
DCM	Dichloromethane	CH_2Cl_2
DIAD	Diisopropyl azodicarboxylate	
DIBALH	Diisobutylaluminum hydride	$HAl(CH_2CH(CH_3)_2)_2$
DMA	Dimethylacetamide	$(CH_3)_2NCOCH_3$
DMAP	4-Dimethylaminopyridine	

DME	1,2-Dimethoxyethane	$ClCH_2CH_2Cl$
DMP	Dess-Martin periodinane	
DMS	Dimethylsulfide	CH_3SCH_3
DMSO	Dimethylsulfoxide	CH_3SOCH_3
Et	Ethyl	$-CH_2CH_3$
HBCat	Catecholborane	
HMPA	Hexamethylphosphoramide	$OP(N(CH_3)_2)_3$ Polar, aprotic solvent
iPr	Isopropyl	$-CH(CH_3)_2$
LDA	Lithium diisopropylamide	Li $N(C(CH_3)_2)_2$
mCPBA	m-Chloroperoxybenzoic acid	
Me	Methyl	$-CH_3$
MOM	Methoxymethyl	
MS	Mesylate	$-SO_2CH_3$
NaHMDS KHMDS LiHMDS	Sodium/Potassium/Lithium hexamethyldisilazide [strong, bulky base]	Na/K/Li $N(Si(CH_3)_3)_2$
NBS/NCS	*N*-Bromosuccinimide/N-Chlorosuccinimide	
nBu	N-butyl	$-CH_2CH_2CH_2CH_3$
NIS	*N*-Iodosuccinimide	
NMO	N-Methylmorpholine N-oxide	
PCC	Pyridinium chlorochromate	
Ph	Phenyl	$-C_6H_5$
PMB	p-Methoxybenzyl	
Piv	Pivaloyl	$-COC(CH_3)_3$

Py	Pyridine	
pTsOH	p-Toluenesulfonic acid	
RT	Room temperature	
TBDMS	Tert-butyldimethylsilyl	$-Si(CH_3)_2C(CH_3)_3$
TBDPS	Tert-butyldiphenylsilyl	$-SiPh_2C(CH_3)_3$
tBu	Tert-butyl	$-C(CH_3)_3$
TEA	Triethylamine	$N(CH_2CH_3)_3$
TES	Triethylsilyl	$-Si(CH_2CH_3)_3$
Tf	Triflate	$-SO_2CF_3$
TFA	Trifluoroacetic acid	HO_2CCF_3
THF	Tetrahydrofuran	
TIPS	Triisopropylsilyl	$-Si(CH(CH_3)_2)_3$

Section 1: Radicals

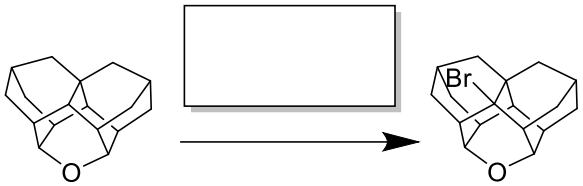
Required foundation for this section:

Free-radical halogenation reactions (chlorination and bromination)

Section 1 - Box-Type Questions

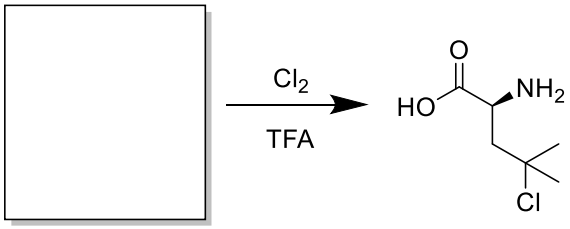
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

1.1.1



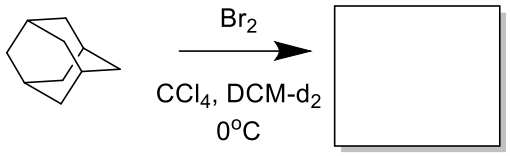
Fokin, A. A.; Zhuk, T. S.; Pashenko, A. E.; Dral, P. O.; Gunchenko, P. A.; Dahl, J. E. P.; Carlson, R. M. K.; Koso, T. V.; Serafin, M.; Schreiner, P. R. Oxygen-Doped Nanodiamonds: Synthesis and Functionalizations. *Org. Lett.* **2009**, *11* (14), 3068–3071. https://doi.org/10.1021/ol901089h

1.1.2



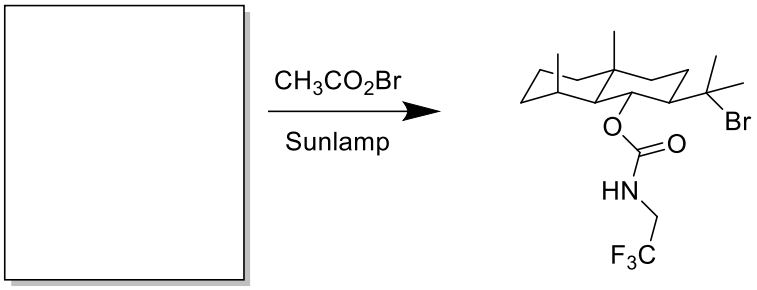
Watts, Z. I.; Easton, C. J. Peculiar Stability of Amino Acids and Peptides from a Radical Perspective. *J. Am. Chem. Soc.* **2009**, *131* (32), 11323–11325. https://doi.org/10.1021/ja9027583

1.1.3



Shernyukov, A. V.; Salnikov, G. E.; Krasnov, V. I.; Genaev, A. M. Cluster Halogenation of Adamantane and Its Derivatives with Bromine and Iodine Monochloride. *Org. Biomol. Chem.* **2022**, *20* (43), 8515–8527. https://doi.org/10.1039/D2OB01455F

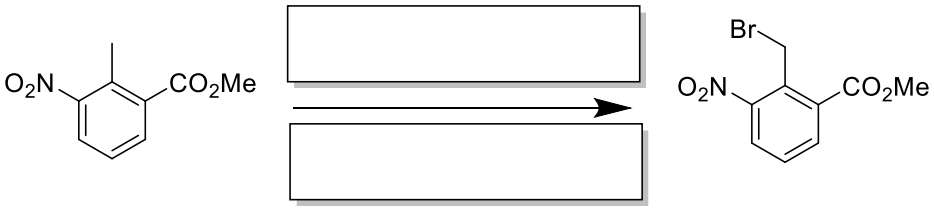
1.1.4



Note: CH_3CO_2Br (Acetyl hypobromite) undergoes a homolytic cleavage to give acyloxy and bromine radicals.

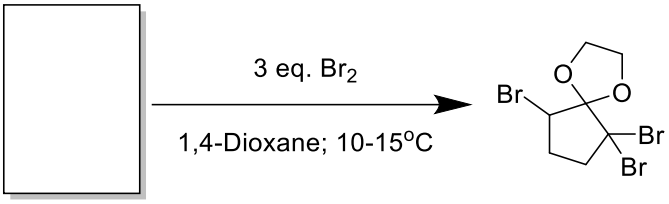
Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* **2009**, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

1.1.5



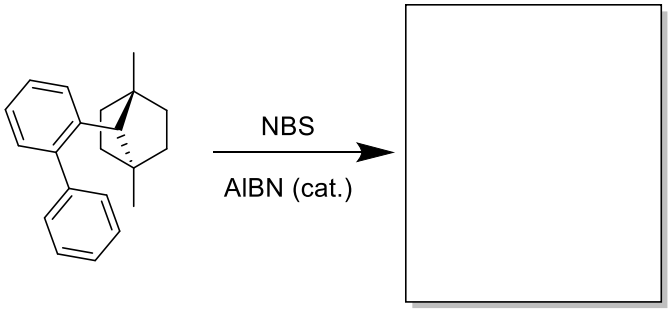
Sharma, K.; Strizhak, A. V.; Fowler, E.; Wang, X.; Xu, W.; Hatt Jensen, C.; Wu, Y.; Sore, H. F.; Lau, Y. H.; Hyvönen, M.; Itzhaki, L. S.; Spring, D. R. Water-Soluble, Stable and Azide-Reactive Strained Dialkynes for Biocompatible Double Strain-Promoted Click Chemistry. *Org. Biomol. Chem.* **2019**, *17* (34), 8014-8018. https://doi.org/10.1039/c9ob01745c

1.1.6



Bartonek, A.; Klapötke, T. M.; Krumm, B. Sensitive 1,4-Disubstituted Nitro-Containing Cubanes: Structures and Properties. *J. Org. Chem.* **2023**, *88* (18), 12884–12890. https://doi.org/10.1021/acs.joc.3c00384

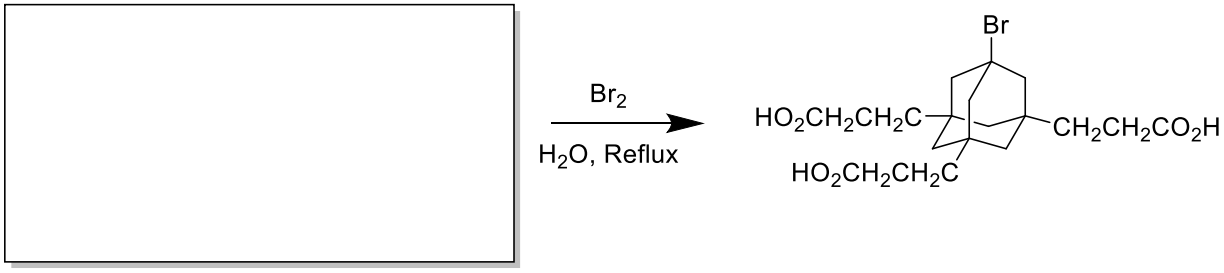
1.1.7



Note: AIBN reacts with NBS to generate a bromine radical.

Gu, Z.; Zeng, T.; Yuan, Z.; et al. Photocatalytic Stereoselective Editing of Alkynes to 3D Molecules via Hydrogen Atom Transfer-Mediated Dynamic Epimerization. *Nat. Commun*. **2026**, *17*, 2518. https://doi.org/10.1038/s41467-026-69219-0

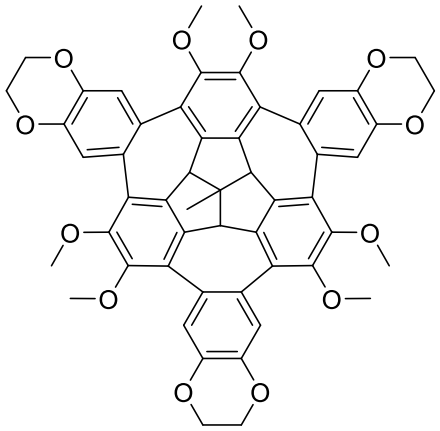
1.1.8



Note: The authors added CH3CN to the reaction mixture to immediately convert the bromo product to an amide.

Maison, W.; Frangioni, J. V.; Pannier, N. Synthesis of Rigid Multivalent Scaffolds Based on Adamantane. *Org. Lett.* **2004**, *6* (24), 4567–4569. https://doi.org/10.1021/ol048055j

1.1.9



Excess Br_2

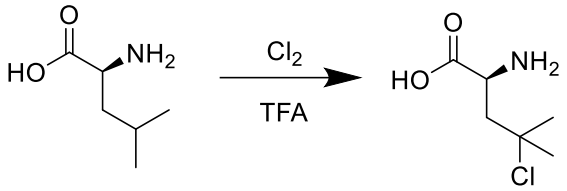
CCl_4, 120°C

Hung, T.; Kuck, D.; Chow, H. Donor-Acceptor Tribenzotriquinacene-Based Molecular Wizard Hats Bearing Three *ortho*-Benzoquinone Units. *Chem. Eur. J. 2023*, **29** (18), e202203749. https://doi.org/10.1002/chem.202203749

Section 1 - Mechanism Questions

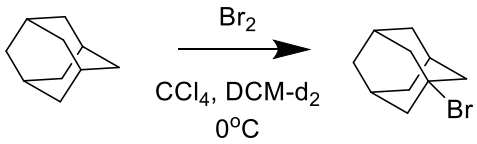
Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

1.2.1



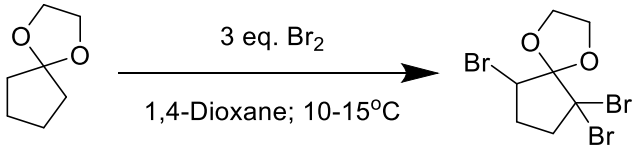
Watts, Z. I.; Easton, C. J. Peculiar Stability of Amino Acids and Peptides from a Radical Perspective. *J. Am. Chem. Soc.* 2009, *131* (32), 11323–11325. https://doi.org/10.1021/ja9027583

1.2.2



Shernyukov, A. V.; Salnikov, G. E.; Krasnov, V. I.; Genaev, A. M. Cluster Halogenation of Adamantane and Its Derivatives with Bromine and Iodine Monochloride. *Org. Biomol. Chem.* 2022, *20* (43), 8515–8527. https://doi.org/10.1039/D2OB01455F

1.2.3



Bartonek, A.; Klapötke, T. M.; Krumm, B. Sensitive 1,4-Disubstituted Nitro-Containing Cubanes: Structures and Properties. *J. Org. Chem.* 2023, *88* (18), 12884–12890. https://doi.org/10.1021/acs.joc.3c00384

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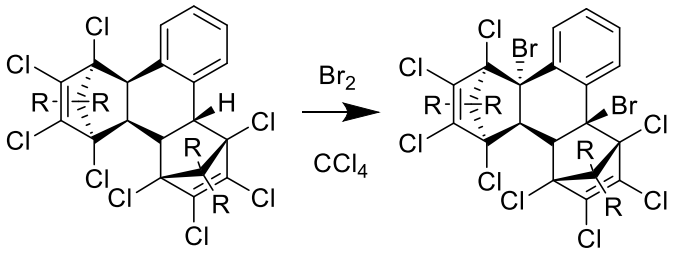

R = -OMe

Shibata, K.; Kulkarni, A. A.; Ho, D. M.; Pascal, R. A. The Pursuit of Perchlorotriphenylene. *J. Org. Chem.* 1995, *60* (2), 428–434. https://doi.org/10.1021/jo00107a023

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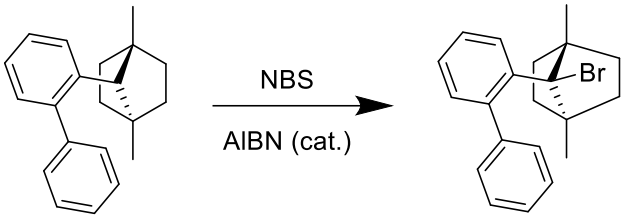
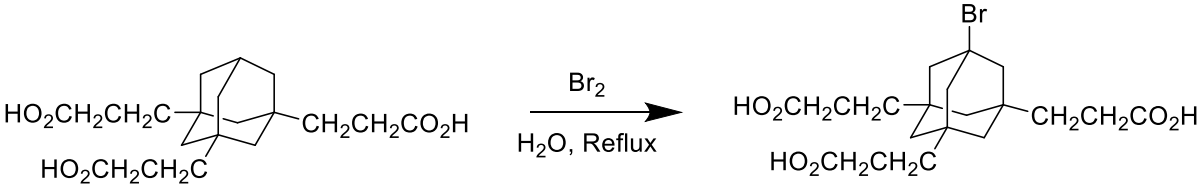


Note: AIBN reacts with NBS to generate a bromine radical.

Gu, Z.; Zeng, T.; Yuan, Z.; et al. Photocatalytic Stereoselective Editing of Alkynes to 3D Molecules via Hydrogen Atom Transfer-Mediated Dynamic Epimerization. *Nat. Commun*. 2026, *17*, 2518. https://doi.org/10.1038/s41467-026-69219-0

1.2.6



Maison, W.; Frangioni, J. V.; Pannier, N. Synthesis of Rigid Multivalent Scaffolds Based on Adamantane. *Org. Lett.* 2004, *6* (24), 4567–4569. https://doi.org/10.1021/ol048055j

Section 2: Nucleophilic Substitution

Required foundation for this section:

Nucleophilic substitution

S_N1

S_N2

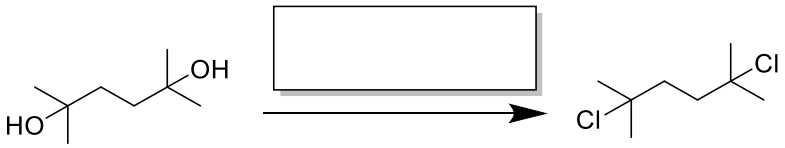
Including Williamson ether synthesis and acid cleavage of ethers

Rearrangements

Section 2 – Box-Type Questions

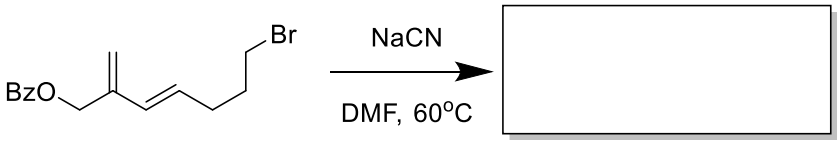
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

2.1.1



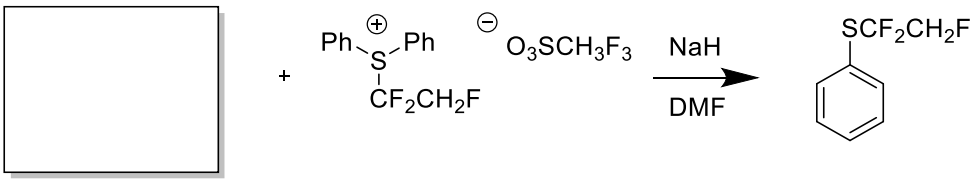
Wagner, C. E.; Marshall, P. A. Synthesis of 2,5-Dichloro-2,5-dimethylhexane by an SN1 Reaction. *J. Chem. Educ*. 2010, *87* (1), 81-83. https://doi.org/10.1021/ed8000057

2.1.2



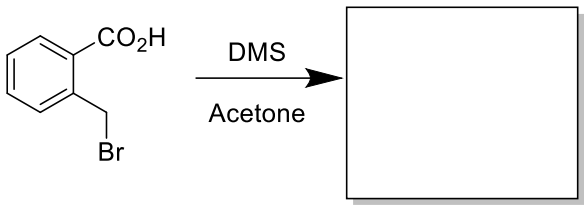
Ratsch, F.; Schmalz, H.-G. An Atom-Economic and Stereospecific Access to Trisubstituted Olefins through Enyne Cross Metathesis Followed by 1,4-Hydrogenation. *Synlett* 2018, *29* (06), 785–792. https://doi.org/10.1055/s-0036-1591528

2.1.3



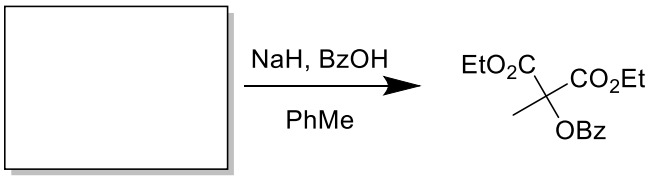
Majumder, S.; Alam, M. N.; Dolbier, W. R. Initial Investigation of the Direct Incorporation of the 1,1,2-Trifluoroethyl Substituent into Organic Compounds. *Org. Lett.* 2025, *27* (20), 5213–5217. https://doi.org/10.1021/acs.orglett.5c01403

2.1.4



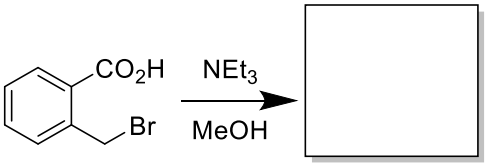
Pan, H.-L.; Kong, H.-H.; Ding, M.-W. One-Pot Synthesis of 3,4-Dihydroisoquinolin-1(2H)-Ones via a Sequential Ugi-4CR and Nucleophilic Substitution Reaction. *Tetrahedron* 2025, *178*, 134609. https://doi.org/10.1016/j.tet.2025.134609

2.1.5



Monerris Mascaro, M.; Henderson, A. P.; Drozdowska, M.; Richardson, R.; Nagel-Savage, D.; Hall, M. J.; Longcake, A.; Mardiana, L.; Golding, B. T. Total Synthesis of 8-Hydroxy-Dihydroergotamine, the Major Human Metabolite of Dihydroergotamine. *Molecules* 2026, *31* (9), 1547. https://doi.org/10.3390/molecules31091547

2.1.6



Pan, H.-L.; Kong, H.-H.; Ding, M.-W. One-Pot Synthesis of 3,4-Dihydroisoquinolin-1(2H)-Ones via a Sequential Ugi-4CR and Nucleophilic Substitution Reaction. *Tetrahedron* 2025, *178*, 134609. https://doi.org/10.1016/j.tet.2025.134609

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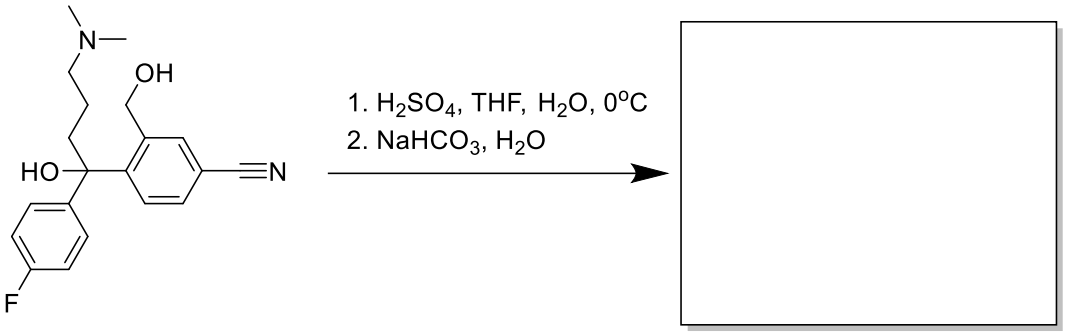
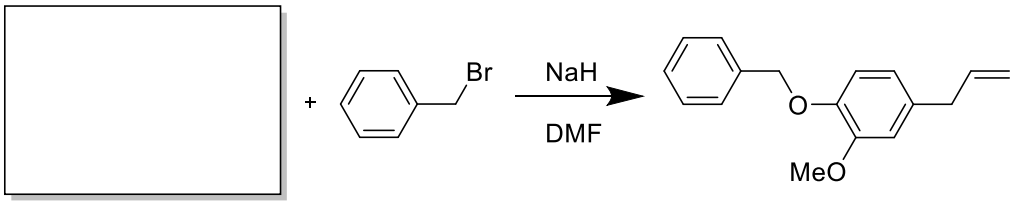


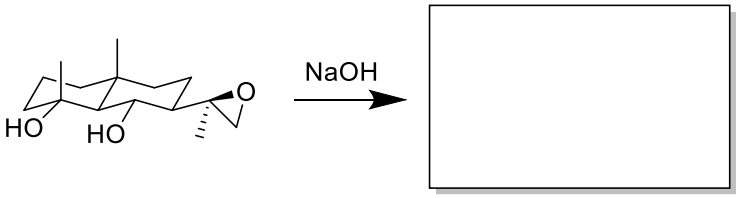
Liu, J.; Zheng, H.-X.; Yao, C.-Z.; Sun, B.-F.; Kang, Y.-B. Pharmaceutical-Oriented Selective Synthesis of Mononitriles and Dinitriles Directly from Methyl(hetero)arenes: Access to Chiral Nitriles and Citalopram. *J. Am. Chem. Soc*. 2016, *138* (10), 3294–3297. https://doi.org/10.1021/jacs.6b00180

2.1.8



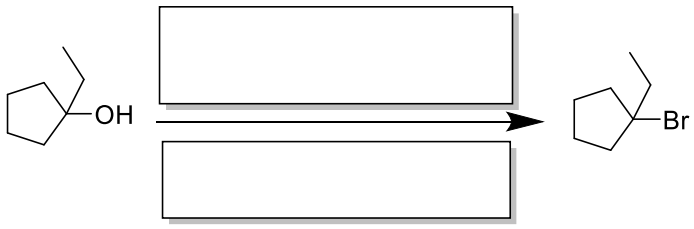
Shet, M. N.; Ramana, C. V. Total Synthesis of (−) and (+)-Zingibergingerols A. *J. Org. Chem.* 2024, *89* (22), 16923–16928. https://doi.org/10.1021/acs.joc.4c01649

2.1.9



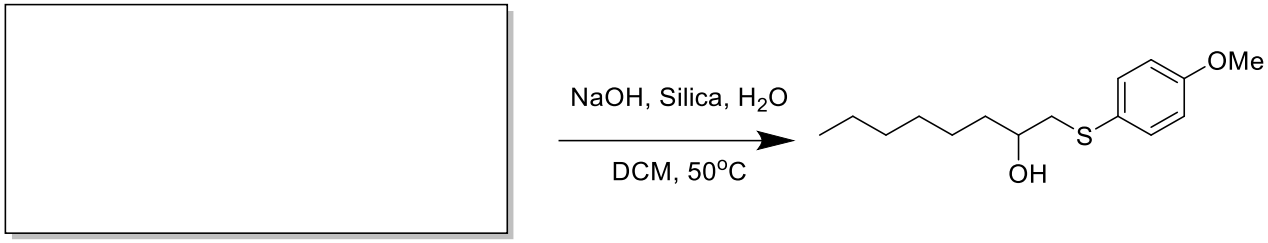
Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* 2009, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

2.1.10



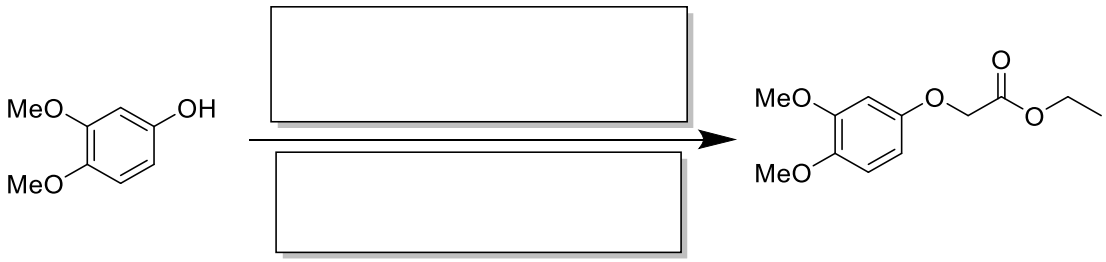
Chevet, L.; Durandetti, M.; Chausset-Boissarie, L. Electrochemical Generation of Alkyl Radicals from Boronic Esters for SOMOphilic Alkynylation. *Org. Lett*. 2026, *28* (5), 1709–1714. https://doi.org/10.1021/acs.orglett.5c05195

2.1.11



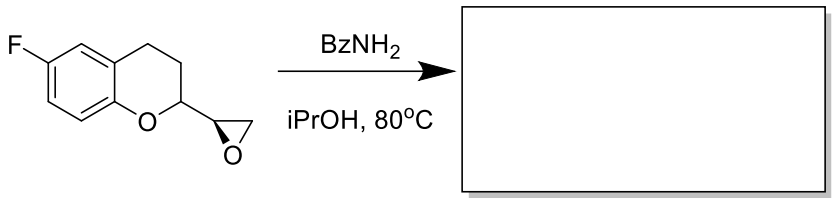
Xie, C.; Wang, Z.; Zhuang, W.; Liu, R.; Shi, C.; Liu, C.; Xu, Y.; Zhao, Y.; Li, X.; Shi, D. Photoinduced 1,2-Chlorothiolation of Unactivated Alkenes via Proton Transfer and Electron Transfer. *Org. Lett.* 2026, *28* (7), 2272–2277. https://doi.org/10.1021/acs.orglett.5c05294

2.1.12



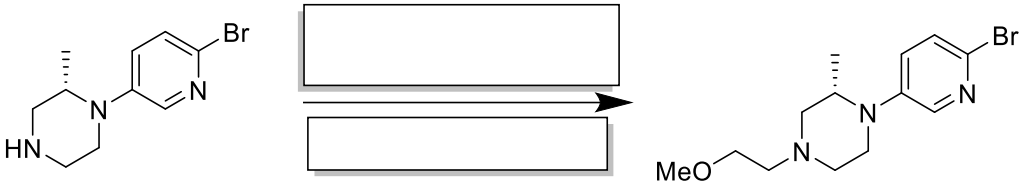
Ding, L.; An, Y.; Li, W.; Shangguan, H.; Tu, H.; Xu, X.; Shi, Y.; Liu, J.; Xie, Y. Design, Synthesis and Evaluation of Bis-3,4-Dimethoxybenzene-Based Fibrate Derivatives Guided by Structural Simplification and Bioisosterism Principle as Potential Hypolipidemic and Hepatoprotective Agents. *Bioorganic Chemistry* 2026, *173*, 109626. https://doi.org/10.1016/j.bioorg.2026.109626

2.1.13



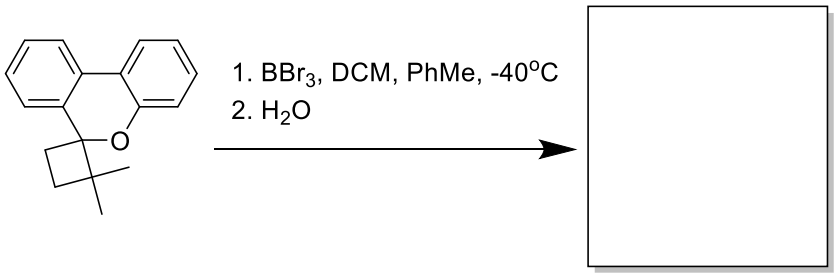
Ghosh, B.; Iglhaut, M.; Babushkina, D.; Pauls, M.; Bannwarth, C.; Bach, T. Photochemical Deracemization of Chromanes and Its Application to the Synthesis of Enantiopure Bioactive Compounds. *Angew. Chem. Int. Ed.* 2026, *65* (5), e21436. https://doi.org/10.1002/anie.202521436

2.1.14



Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* 2026, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

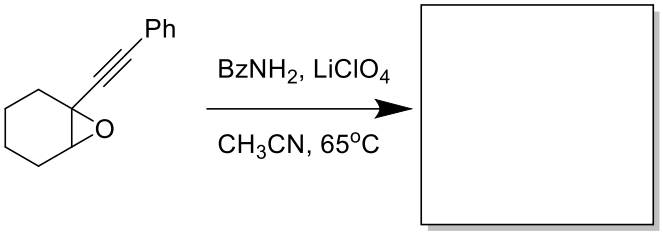
2.1.15



Hint: BBr_3 is a Lewis acid but also a source of bromide.

Geng, B.-H.; Hao, Z.-F.; Lu, Y.-H.; Liu, X.-L.; Li, A.-H.; Tian, P.; Li, Q.-H. Hexafluoroisopropanol-Enabled Access to Spirocyclobutanes via Cyclopropylcarbinyl Cation Rearrangement. *Org. Lett*. 2026, *28* (10), 3243–3248. https://doi.org/10.1021/acs.orglett.6c00248

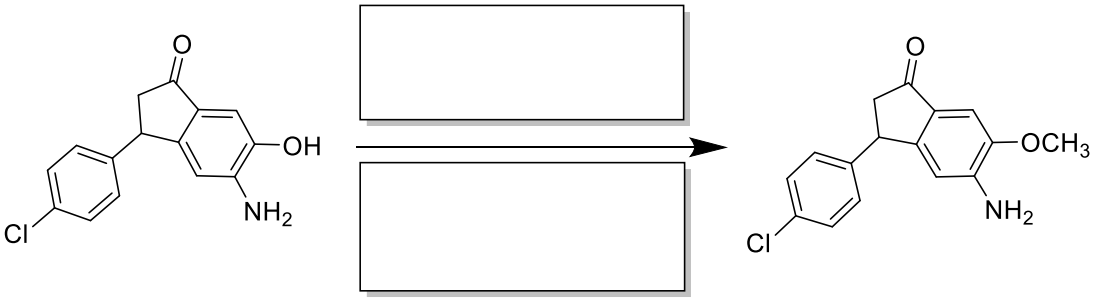
2.1.16



Note: For introductory organic chemistry courses, you can ignore the $LiClO_4$.

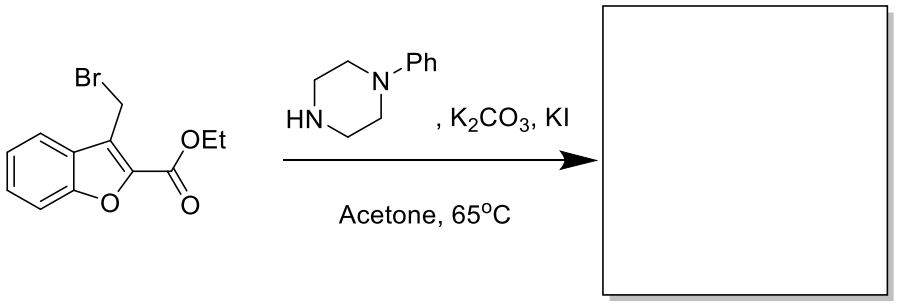
Belov, D. S.; Lukyanenko, E. R.; Kurkin, A. V.; Yurovskaya, M. A. Highly Stereoselective and Scalable Synthesis of *Trans* -Fused Octahydrocyclohepta[*b*]Pyrrol-4(1 *H*)-Ones via the Aza-Cope–Mannich Rearrangement in Racemic and Enantiopure Forms. *J. Org. Chem.* 2012, *77* (22), 10125–10134. https://doi.org/10.1021/jo301762a

2.1.17



Park, C. H.; Siomboing, X.; Yous, S.; Gressier, B.; Luyckx, M.; Chavatte, P. Investigations of New Lead Structures for the Design of Novel Cyclooxygenase-2 Inhibitors. *Eur. J. Med. Chem.* 2002, *37* (6), 461–468. https://doi.org/10.1016/S0223-5234(02)01373-9.

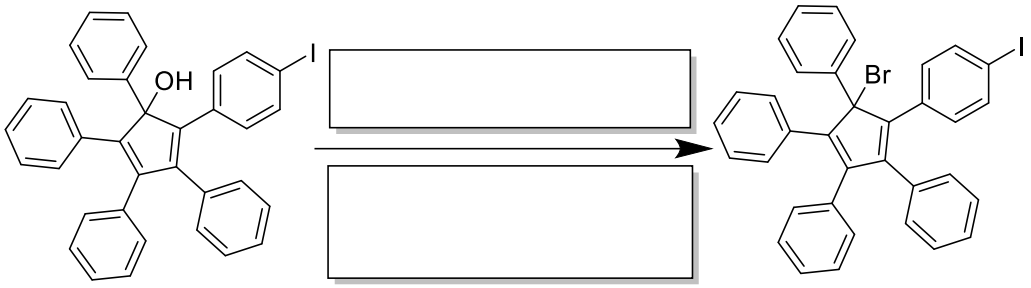
2.1.18



Eldehna, W. M.; Tawfik, H. O.; Nafie, M. S.; Al Kamaly, O.; El-Hamaky, A. A.; El Hassab, M. A.; Elsayed, Z. M.; Elnaggar, Y. S. R.; Al-Karmalawy, A. A.; di Giacomo, V.; Balaha, M. Novel Benzofuran-Conjugated

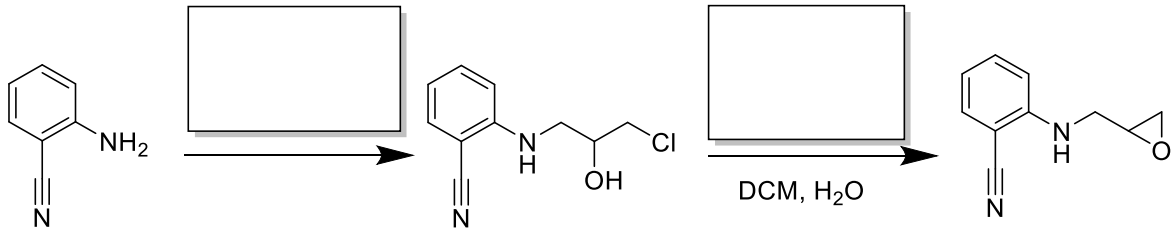
Indolin-2-ones as Anticancer Agents: Design, Synthesis, Biological Assessments, and Molecular Modeling Insights. *Bioorg. Chem.* 2025, *160,* 108494. https://doi.org/10.1016/j.bioorg.2025.108494

2.1.19



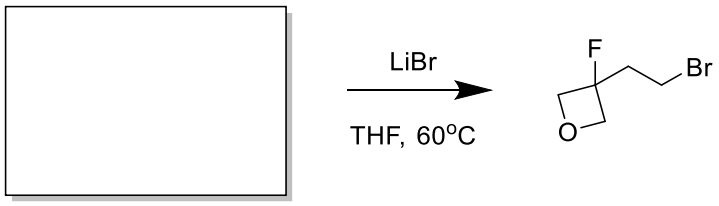
Nishino, T.; Ohno, Y.; Ishihara, M.; Nishikawa, Y.; Martin, C. J.; Yasuhara, K.; Rapenne, G. An Amphiphilic Pentaaryl Cyclopentadienyl Ruthenium(II) Molecular Rotor with a Luminescent Tag. *Synlett* 2025, *36* (9), 1237–1241. https://doi.org/10.1055/a-2503-7748

2.1.20



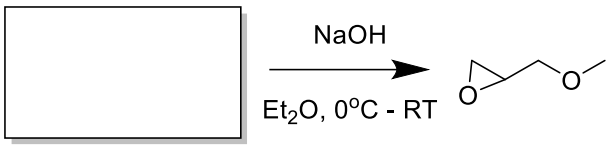
Lee, K.; Lee, X.; Zhou, C.-Y.; Chu, Y.-L.; Lin, C.-K. *Tert* -Butyl Carbonate as a Nucleophile in Epoxide Ring Opening: A Cascade Synthesis of 5-(Hydroxymethyl)Oxazolidin-2-One. *J. Org. Chem.* 2025, *90* (23), 7976–7981. https://doi.org/10.1021/acs.joc.5c00537

2.1.21



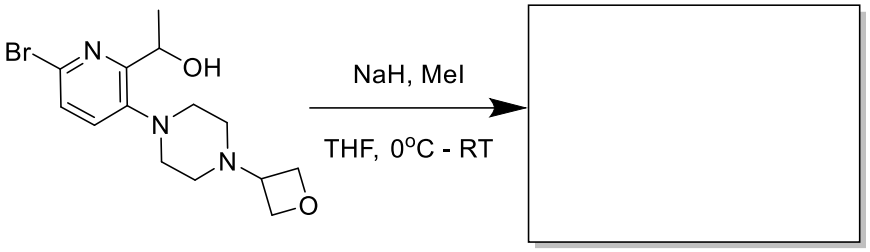
Litskan, E. V.; Lynnyk, S. V.; Shypov, R. H.; Vashchenko, B. V.; Hoida, A. Ye.; Klymenko-Ulianov, O. O.; Gorlova, A. O.; Granat, D. S.; Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V. Fine-Tuning of Physicochemical Properties of 3,3-Disubstituted Oxetanes Introducing Fluorine Atom(s) on the Building Blocks Level. *Chem. Eur. J.* 2025, *31* (51), e202500940. https://doi.org/10.1002/chem.202500940

2.1.22



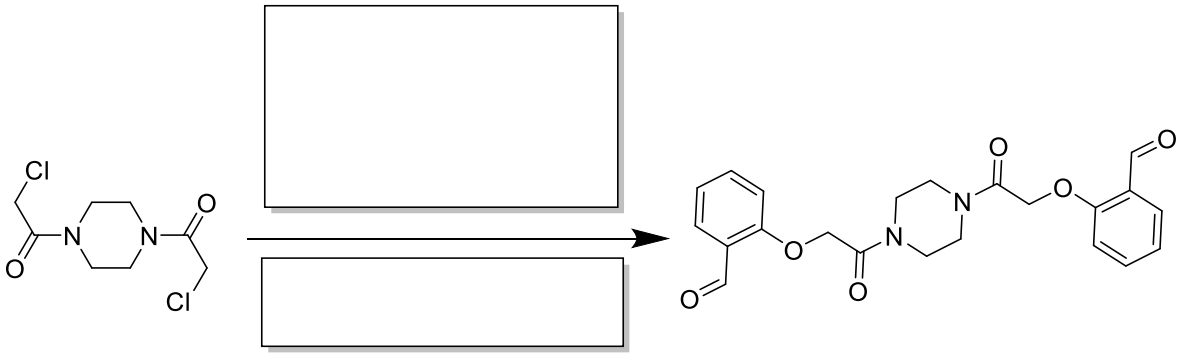
Mironov, V. F.; Nemtarev, A. V.; Tsepaeva, O. V.; Dimukhametov, M. N.; Litvinov, I. A.; Voloshina, A. D.; Pashirova, T. N.; Titov, E. A.; Lyubina, A. P.; Amerhanova, S. K.; Gubaidullin, A. T.; Islamov, D. R. Rational Design 2-Hydroxypropylphosphonium Salts as Cancer Cell Mitochondria-Targeted Vectors: Synthesis, Structure, and Biological Properties. *Molecules* 2021, *26* (21), 6350. https://doi.org/10.3390/molecules26216350

2.1.23



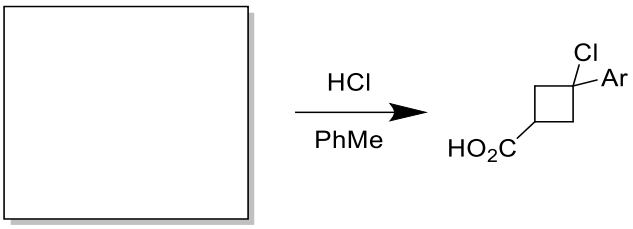
Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* 2026, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

2.1.24



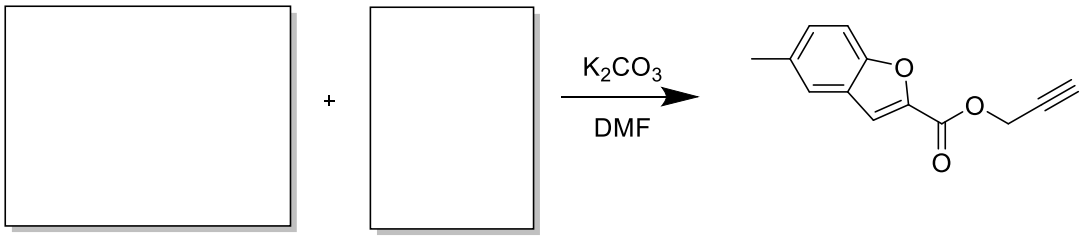
Alsulami, M. R.; Salem, M. E.; Abdelhamid, I. A.; Elwahy, A. H. M.; Barakat, K.; Abdelmoniem, A. M.; Raza, N.; Abdelwahab, R. E. Novel Bis(1,3,4a,9-Tetraza-4H-Fluoren-2-Amine) Derivatives: Synthesis, Antibacterial Activities, and Molecular Docking. *J. Mol. Struct.* 2026, *1349*, 143904. https://doi.org/10.1016/j.molstruc.2025.143904

2.1.25



Hazra, S.; Patel, M.; Mondal, S.; Ahmed, R.; Sasmal, P.; De, S.; Saha, J. Lewis Acid Catalyzed Dual Strain-Release Platform for Transforming Azabicyclo[1.1.0]butanes into Functionalized Azetidines with Donor-Acceptor (D-A) Cyclopropanes and Bicyclo[1.1.0]butanes. *Org. Lett.* 2026, *28* (14), 4554-4559. https://doi.org/10.1021/acs.orglett.6c00880

2.1.26

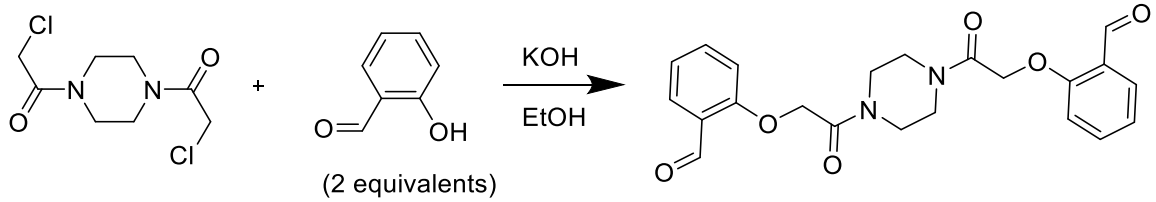


Sulakhe, S. M.; Khanzode, A. K.; Jamale, S. E.; Singh, M. B.; Singh, P.; Kumari, J.; Sriram, D.; Vedpathak, S. G.; Haval, K. P. New Benzofuran-Triazole-Tetrazole Conjugates: Synthesis, Antitubercular Evaluation, Molecular Docking, DFT, and MD Simulation. *J. Mol. Struct*. 2027, *1379*, 147348. https://doi.org/10.1016/j.molstruc.2026.147348

Section 2 – Mechanism Questions

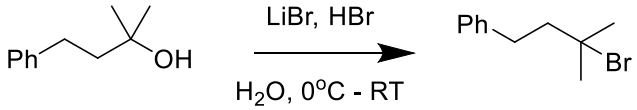
Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

2.2.1



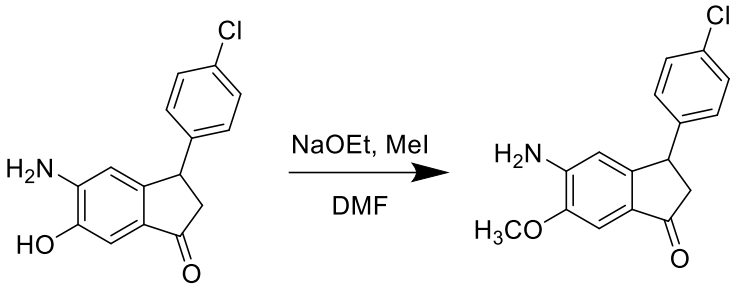
Alsulami, M. R.; Salem, M. E.; Abdelhamid, I. A.; Elwahy, A. H. M.; Barakat, K.; Abdelmoniem, A. M.; Raza, N.; Abdelwahab, R. E. Novel Bis(1,3,4a,9-Tetraza-4H-Fluoren-2-Amine) Derivatives: Synthesis, Antibacterial Activities, and Molecular Docking. *J. Mol. Struct.* 2026, *1349*, 143904. https://doi.org/10.1016/j.molstruc.2025.143904

2.2.2



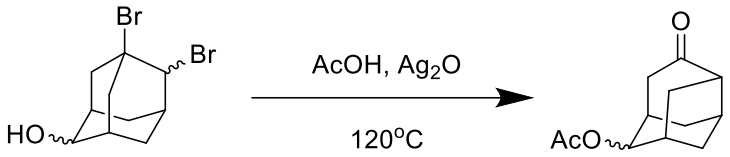
Lu, S.; Chen, L.; Nomura, S.; Isozaki, K.; Nakamura, M. Iron-Catalyzed Radical Cascade Multicomponent Coupling: Expedient Synthesis of Diverse Allenes from 1,3-Enynes. *J. Org. Chem.* 2026, *91* (1), 71–86. https://doi.org/10.1021/acs.joc.5c01751

2.2.3



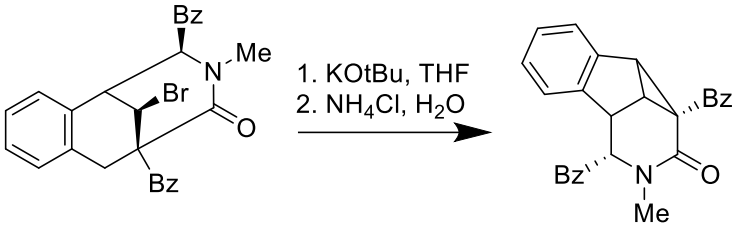
Park, C. H.; Siomboing, X.; Yous, S.; Gressier, B.; Luyckx, M.; Chavatte, P. Investigations of New Lead Structures for the Design of Novel Cyclooxygenase-2 Inhibitors. *Eur. J. Med. Chem.* 2002, *37* (6), 461–468. https://doi.org/10.1016/S0223-5234(02)01373-9

2.2.4



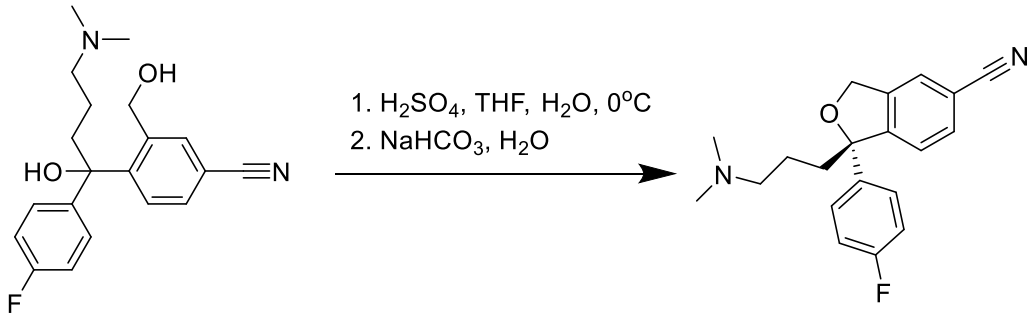
Wang, X.; Dong, Y.; Ezell, E. L.; Garrison, J. C.; Wood, J. K.; Hagen, J. P.; Vennerstrom, J. L. Semipinacol and Protoadamantane-Adamantane Rearrangements of 5,6-Dibromoadamantan-2-One and -2-Ol. *Tetrahedron* 2017, *73* (20), 2972–2976. https://doi.org/10.1016/j.tet.2017.04.006

2.2.5



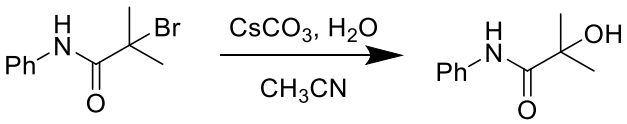
Sośnicki, J. G.; Idzik, T. J.; Borzyszkowska, A.; Maciejewska, G.; Struk, Ł. Synthesis of Polycyclic δ-Lactams with Bridged Benzomorphan Skeleton: Selectivity and Diversity Driven by Substituents. *J. Org. Chem*. 2018, *83* (4), 1745–1760. https://doi.org/10.1021/acs.joc.7b02509

2.2.6



Liu, J.; Zheng, H.-X.; Yao, C.-Z.; Sun, B.-F.; Kang, Y.-B. Pharmaceutical-Oriented Selective Synthesis of Mononitriles and Dinitriles Directly from Methyl(hetero)arenes: Access to Chiral Nitriles and Citalopram. *J. Am. Chem. Soc*. 2016, *138* (10), 3294–3297. https://doi.org/10.1021/jacs.6b00180

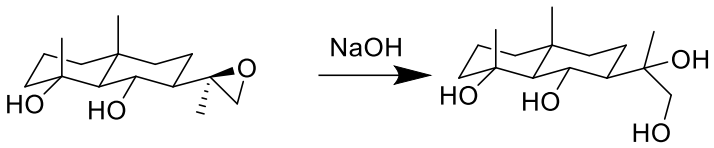
2.2.7



Hint: It is possible to propose a mechanism for this reaction without the participation of the N. The authors proposed a mechanism involving the N. See if you can figure out how it can participate.

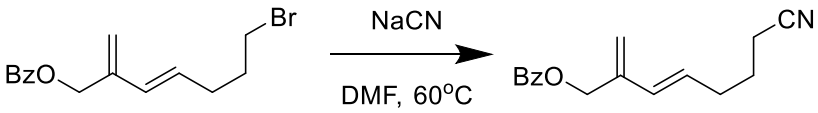
Jiang, Y.; Wu, L.; Wang, C. A Mild Protocol for Highly Congested and Functionalized C(Sp^3)–N Bonds Construction. *J. Org. Chem.* 2026, *91* (7), 2998–3006. https://doi.org/10.1021/acs.joc.5c02608

2.2.8



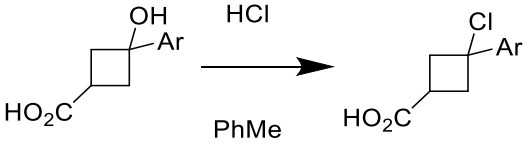
Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* 2009, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

2.2.9



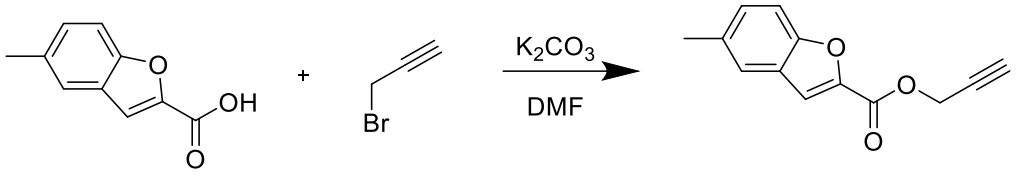
Ratsch, F.; Schmalz, H.-G. An Atom-Economic and Stereospecific Access to Trisubstituted Olefins through Enyne Cross Metathesis Followed by 1,4-Hydrogenation. *Synlett* 2018, *29* (06), 785–792. https://doi.org/10.1055/s-0036-1591528

2.2.10



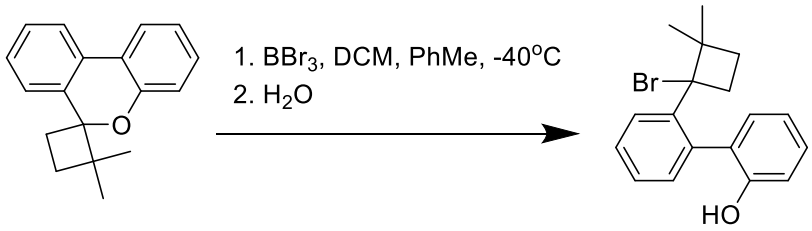
Hazra, S.; Patel, M.; Mondal, S.; Ahmed, R.; Sasmal, P.; De, S.; Saha, J. Lewis Acid Catalyzed Dual Strain-Release Platform for Transforming Azabicyclo[1.1.0]butanes into Functionalized Azetidines with Donor-Acceptor (D-A) Cyclopropanes and Bicyclo[1.1.0]butanes. *Org. Lett.* 2026, *28* (14), 4554-4559. https://doi.org/10.1021/acs.orglett.6c00880

2.2.11



Sulakhe, S. M.; Khanzode, A. K.; Jamale, S. E.; Singh, M. B.; Singh, P.; Kumari, J.; Sriram, D.; Vedpathak, S. G.; Haval, K. P. New Benzofuran-Triazole-Tetrazole Conjugates: Synthesis, Antitubercular Evaluation, Molecular Docking, DFT, and MD Simulation. *J. Mol. Struct*. 2027, *1379*, 147348. https://doi.org/10.1016/j.molstruc.2026.147348

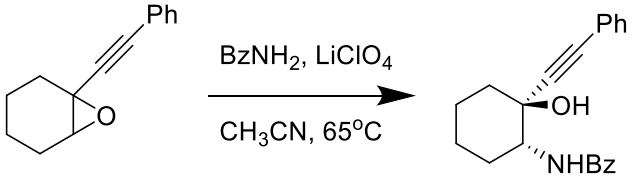
2.2.12



Hint: BBr_3 is a Lewis acid but also a source of bromide.

Geng, B.-H.; Hao, Z.-F.; Lu, Y.-H.; Liu, X.-L.; Li, A.-H.; Tian, P.; Li, Q.-H. Hexafluoroisopropanol-Enabled Access to Spirocyclobutanes via Cyclopropylcarbinyl Cation Rearrangement. *Org. Lett*. 2026, *28* (10), 3243–3248. https://doi.org/10.1021/acs.orglett.6c00248

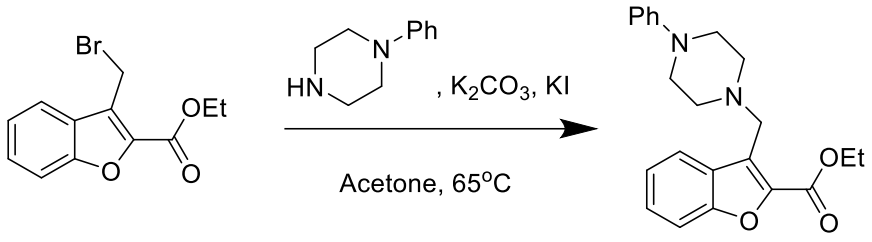
2.2.13



Note: For introductory organic chemistry courses, you can ignore the LiClO4.

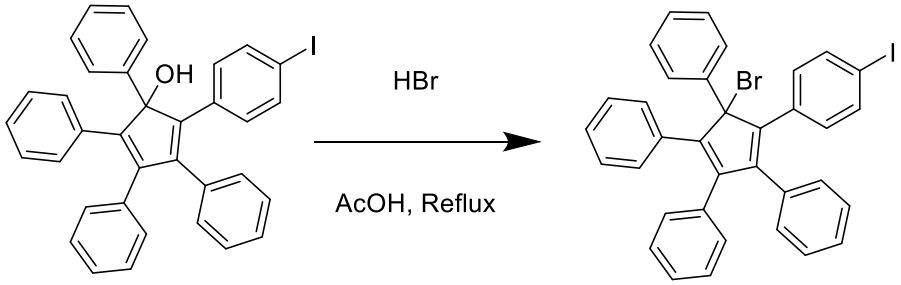
Belov, D. S.; Lukyanenko, E. R.; Kurkin, A. V.; Yurovskaya, M. A. Highly Stereoselective and Scalable Synthesis of *Trans* -Fused Octahydrocyclohepta[*b*]Pyrrol-4(1 *H*)-Ones via the Aza-Cope–Mannich Rearrangement in Racemic and Enantiopure Forms. *J. Org. Chem.* 2012, *77* (22), 10125–10134. https://doi.org/10.1021/jo301762a

2.2.14



Eldehna, W. M.; Tawfik, H. O.; Nafie, M. S.; Al Kamaly, O.; El-Hamaky, A. A.; El Hassab, M. A.; Elsayed, Z. M.; Elnaggar, Y. S. R.; Al-Karmalawy, A. A.; di Giacomo, V.; Balaha, M. Novel Benzofuran-Conjugated Indolin-2-ones as Anticancer Agents: Design, Synthesis, Biological Assessments, and Molecular Modeling Insights. *Bioorg. Chem.* 2025, *160,* 108494. https://doi.org/10.1016/j.bioorg.2025.108494

2.2.15



Nishino, T.; Ohno, Y.; Ishihara, M.; Nishikawa, Y.; Martin, C. J.; Yasuhara, K.; Rapenne, G. An Amphiphilic Pentaaryl Cyclopentadienyl Ruthenium(II) Molecular Rotor with a Luminescent Tag. *Synlett* 2025, *36* (9), 1237–1241. https://doi.org/10.1055/a-2503-7748

Section 3: Elimination

Required foundation for this section:

Elimination

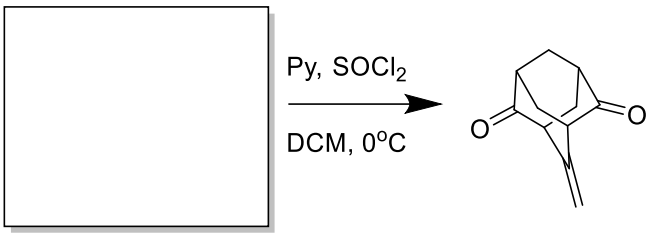
E1

E2

Section 3 – Box-Type Questions

For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

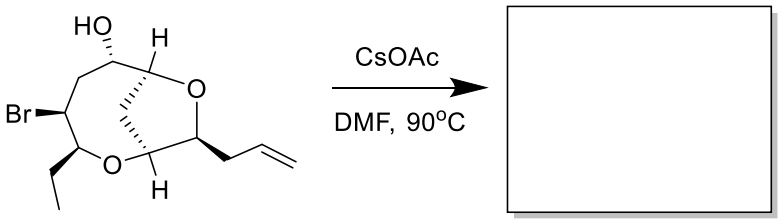
3.1.1



Hint: $SOCl_2$ converts an OH group into a Cl. Treat Py as a bulky base.

Ling, Y.; Zhang, P.; Sun, L.; Lai, W.; Luo, J. Efficient Synthesis of 2,2,4,4,6,6-Hexanitroadamantane under Mild Conditions. *Synthesis* 2014, *46* (16), 2225–2233. https://doi.org/10.1055/s-0033-1341251

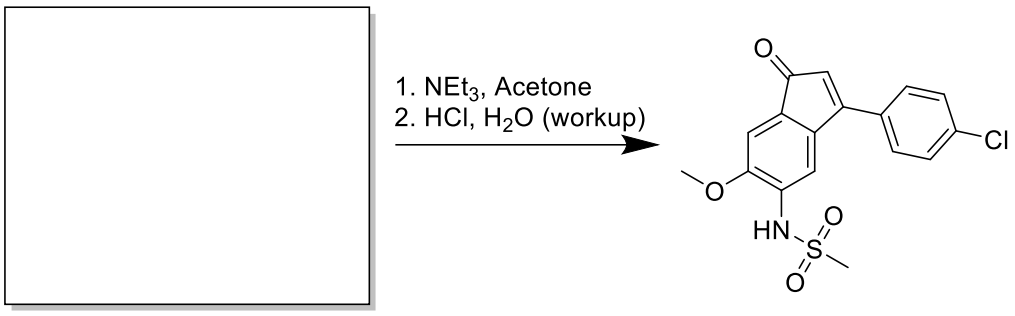
3.1.2



Chan, H. S. S.; Thompson, A. L.; Christensen, K. E.; Burton, J. W. Forwards and Backwards – Synthesis of *Laurencia* Natural Products Using a Biomimetic and Retrobiomimetic Strategy Incorporating Structural

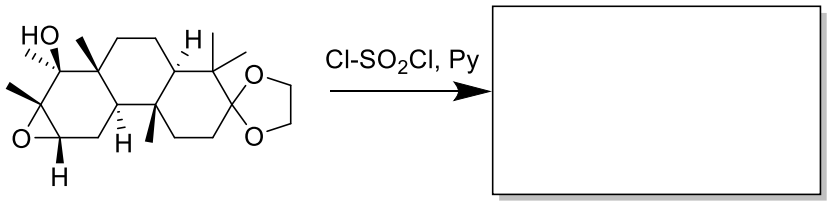
Reassignment of Laurefurenynes C–F. *Chem. Sci.* 2020, *11* (42), 11592–11600. https://doi.org/10.1039/D0SC04120C

3.1.3



Park, C. H.; Siomboing, X.; Yous, S.; Gressier, B.; Luyckx, M.; Chavatte, P. Investigations of New Lead Structures for the Design of Novel Cyclooxygenase-2 Inhibitors. *Eur. J. Med. Chem.* 2002, *37* (6), 461–468. https://doi.org/10.1016/S0223-5234(02)01373-9

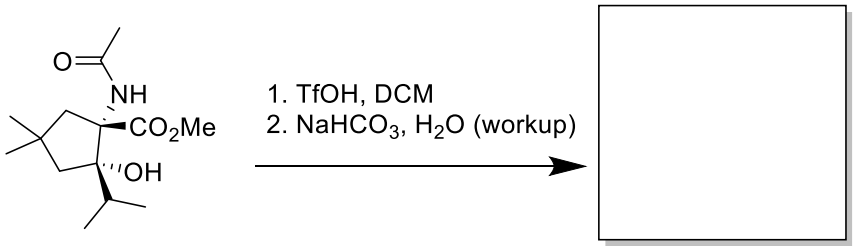
3.1.4



Note: SO_2Cl_2 is analogous to $SOCl_2$.

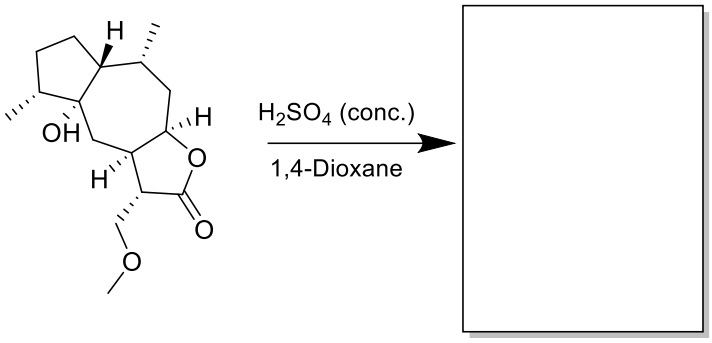
Takikawa, H.; Hirooka, M.; Sasaki, M. The First Synthesis of (±)-Brevione B, an Allelopathic Agent Isolated from Penicillium Sp. *Tetrahedron Lett.* 2003, *44* (28), 5235–5238. https://doi.org/10.1016/S0040-4039(03)01275-9

3.1.5



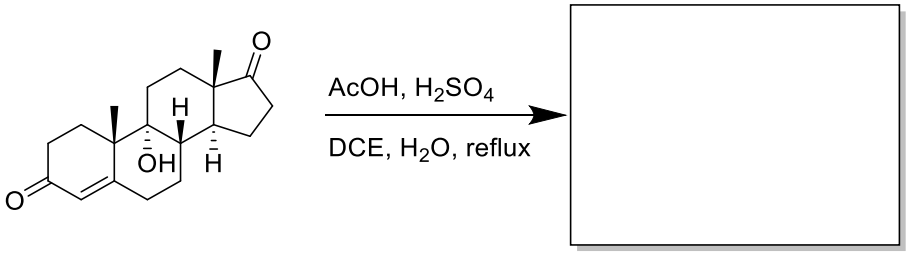
Yamamoto, R.; Qi, X.; Tsukiji, K.; Kwon, E.; Shi, L.; Yoshikai, N. Redox-Neutral Radical−Polar Crossover [3+2] Annulation of Cyclopropanols and Alkenes. *ACS Catalysis* 2026, *16* (9), 7972–7978. https://doi.org/10.1021/acscatal.6c01346

3.1.6



Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* 2024, *26* (22), 4648–4653. https://doi.org/10.1021/acs.orglett.4c01374

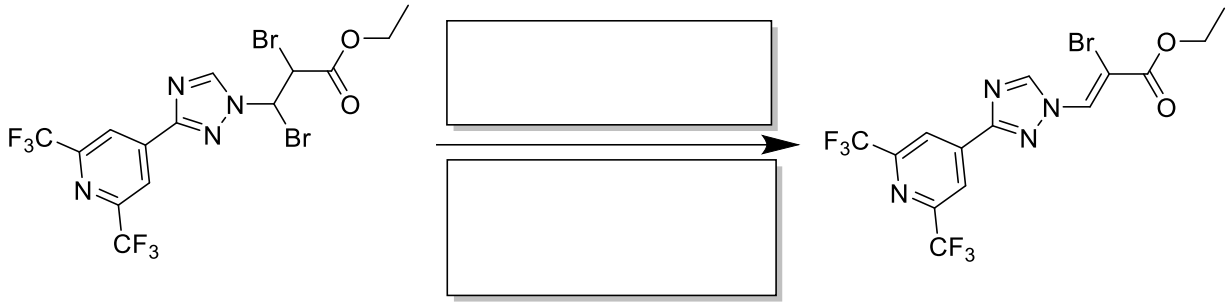
3.1.7



Hint: The product is not what you may expect to be the most stable product.

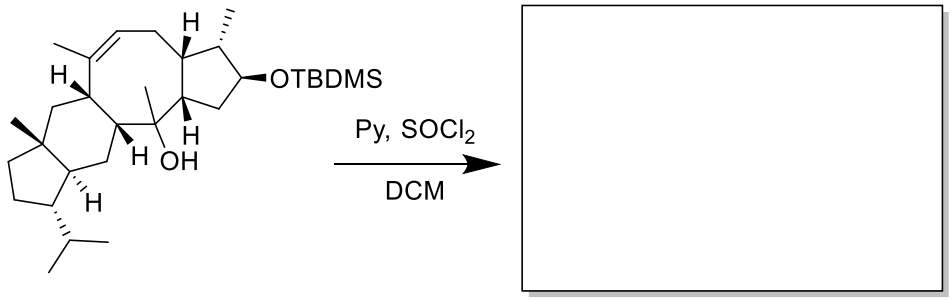
Wei, J.; Zhang, Y.; Liu, M.; Ning, Y.; Cao, Y.; Chen, F. Divergent Chemo- and Biocatalytic Route to 16 *β* -Methylcorticoids: Asymmetric Synthesis of Betamethasone Dipropionate, Clobetasol Propionate, and Beclomethasone Dipropionate. *Angew. Chem. Int. Ed.* 2024, *63* (4), e202313952. https://doi.org/10.1002/anie.202313952

3.1.8



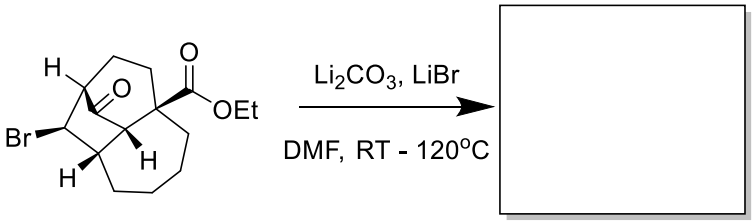
Miao, H.; Qin, Y.; Shao, D.; Chen, Q.; Pan, Y.; Lei, M.; Wu, R.; Ye, X.; Wang, X.; Zhu, Y. Discovery of SZJK-0421: A Novel Potent, Low Toxicity, Selective Second Generation of CRM1 Inhibitor for the Treatment of Both Hematological and Solid Tumors. *J. Med. Chem.* 2024, *67* (22), 20595–20618. https://doi.org/10.1021/acs.jmedchem.4c02169

3.1.9



Paquette, L. A. Studies Directed to the Synthesis of the Antifungal Antibiotic Aleurodiscal. Enantioselective Construction of an Advanced β-D-Xyloside Congener. *Synthesis* 1998, *1998* (Spec. Issue), 495-508. https://doi.org/10.1055/s-1998-5921

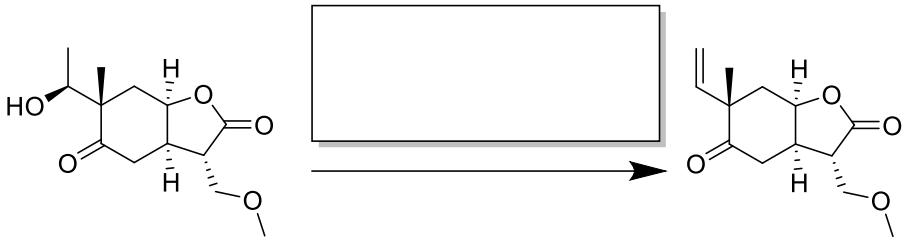
3.1.10



Hint: The bromide of LiBr does a substitution reaction first.

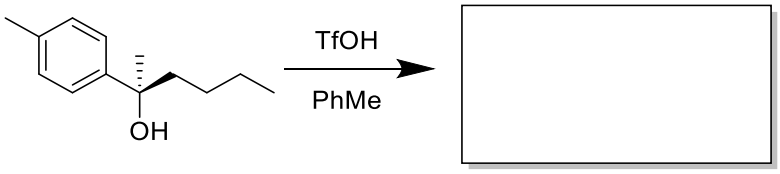
Cao, S.-Y.; Yue, H.-J.; Zhu, M.-Q.; Xu, L. Synthesis of Tricyclo[7.2.1.0^{9,10}]Dodecan-11-One Core Ring Systems of Norditerpenoid Alkaloids and Racemulosine. *Org. Chem. Front.* 2020, *7* (7), 933–937. https://oi.org/10.1039/D0QO00088D

3.1.11



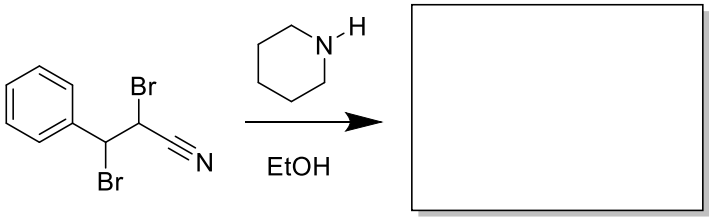
Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* 2024, *26* (22), 4648–4653. https://doi.org/10.1021/acs.orglett.4c01374

3.1.12



Kavanagh, S. E.; Monasterolo, C.; Gilheany, D. G. Enantiospecific Acid-Catalysed Hydroperoxidation of Scalemic Tertiary Benzylic Alcohols Facilitating a Concise Asymmetric Synthesis of Yingzhaosu C. *Eur. J. Org. Chem.* 2026, *29* (26), e70581. https://doi.org/10.1002/ejoc.70581

3.1.13

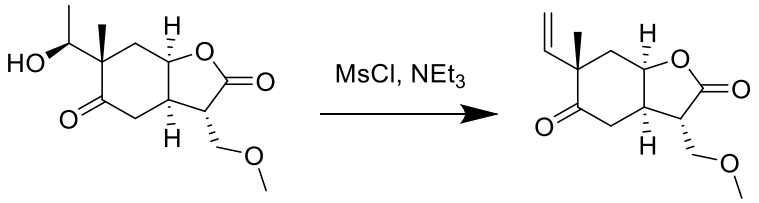


Thibonnet, J.; Vu, V. A.; Bérillon, L.; Knochel, P. Preparation of α-Functionalized Alkenylmagnesium Reagents via a Halide−Magnesium Exchange. *Tetrahedron* 2002, *58* (24), 4787–4799. https://doi.org/10.1016/S0040-4020(02)00439-8

Section 3 – Mechanism Questions

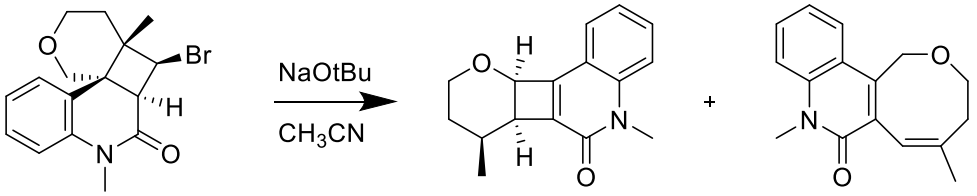
Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

3.2.1



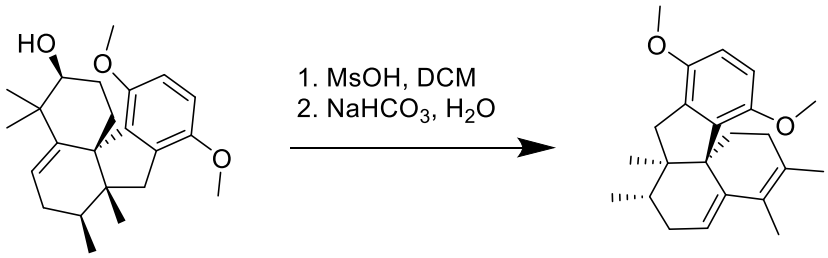
Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* 2024, *26* (22), 4648–4653. https://doi.org/10.1021/acs.orglett.4c01374

3.2.2



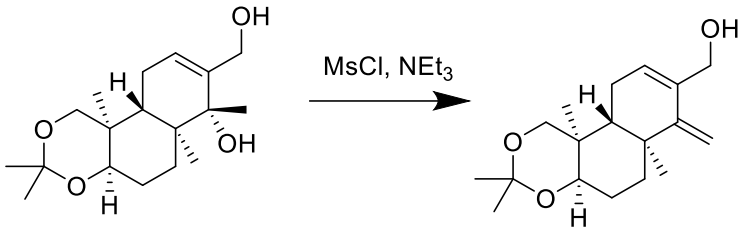
Pan, G.; Qin, S.; Xu, D.; Kühn, F. E.; Guo, H. Visible Light-Induced Pericyclic Cascade Reaction for the Synthesis of Quinolinone Derivatives with an Oxabicyclo[4.2.0]octene Skeleton. *Org. Lett*. 2021, *23* (8), 2959–2963. https://doi.org/10.1021/acs.orglett.1c00642

3.2.3



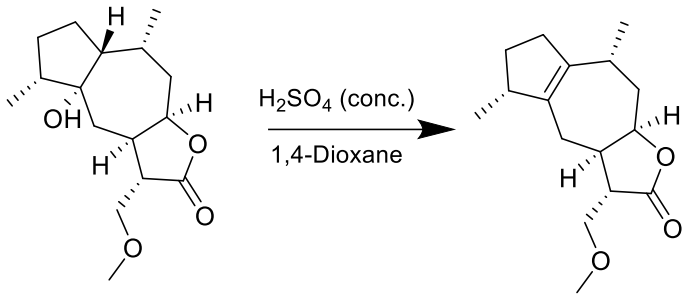
Chong, C.; Chang, L.; Grimm, I.; Zhang, Q.; Kuang, Y.; Wang, B.; Kang, J.; Liu, W.; Baars, J.; Guo, Y.; Schmalz, H.-G.; Lu, Z. Divergent Total Synthesis of the Revised Structures of Marine Anti-Cancer Meroterpenoids (+)-Dysiherbols A-E. *Chem. Sci.* 2023. *14* (12). 3302-3310. https://doi.org/10.1039/d3sc00173c

3.2.4



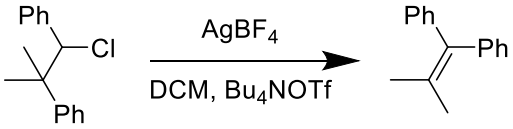
Hayward Cooke, J.; Jamshed, S.; Sarpong, R. Synthetic Studies toward the Aphidicolin Family of Diterpenoid Natural Products. *J. Org. Chem.* 2025, *90* (28), 9999–10016. https://doi.org/10.1021/acs.joc.5c01047

3.2.5



Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* 2024, *26* (22), 4648–4653. https://doi.org/10.1021/acs.orglett.4c01374

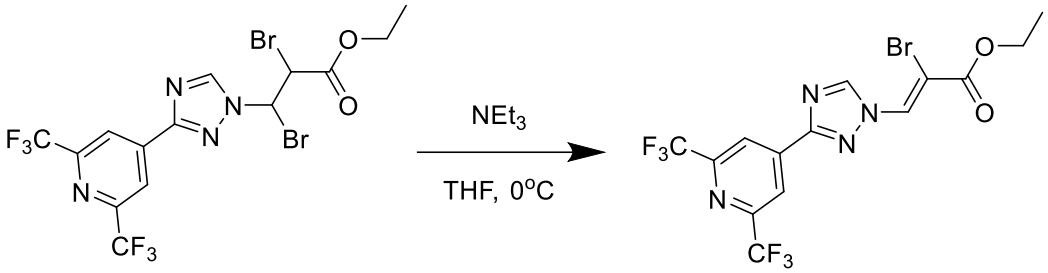
3.2.6



Note: $AgBF_4$ facilitates the dissociation of Cl^-.

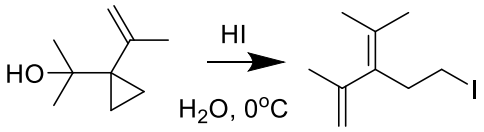
Alfonso, V. G.; de la Vega-Hernández, K.; Suero, M. G. Single-Carbon Insertion into Single C-C Bonds with Diazirines. *J. Am. Chem. Soc.* 2025, *147* (1), 57-62. https://doi.org/10.1021/jacs.4c12632

3.2.7



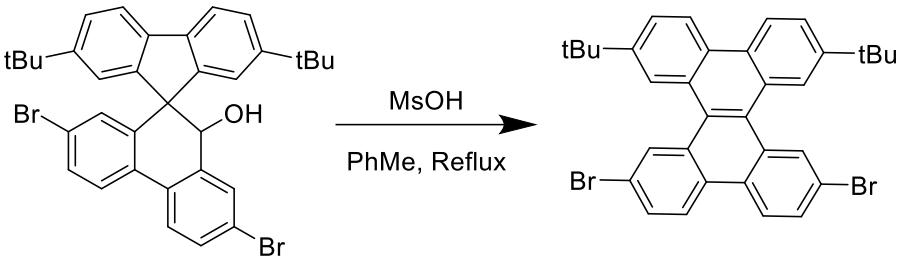
Miao, H.; Qin, Y.; Shao, D.; Chen, Q.; Pan, Y.; Lei, M.; Wu, R.; Ye, X.; Wang, X.; Zhu, Y. Discovery of SZJK-0421: A Novel Potent, Low Toxicity, Selective Second Generation of CRM1 Inhibitor for the Treatment of Both Hematological and Solid Tumors. *J. Med. Chem.* 2024, *67* (22), 20595–20618. https://doi.org/10.1021/acs.jmedchem.4c02169

3.2.8



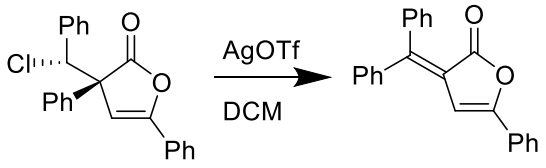
Espinoza-Hicks, J. C.; Zaragoza-Galán, G.; Camacho-Dávila, A. A. A Practical Synthesis of Homoallylic Diene Halides: Versatile Synthons for the Preparation of the Taxane A-Ring System. *Synthesis* 2024, *56* (2), 239-242. https://doi.org/10.1055/a-2215-3546

3.2.9



Yoshida, N.; Akasaka, R.; Yamaoka, Y.; Yashima, T.; Tokunaga, Y.; Iwasawa, T. Cross-Dimerization of Fluorenones for Synthesis of Dibenzo[*g,p*]chrysenes. *Tetrahedron* 2023, *143*, 133549. https://doi.org/10.1016/j.tet.2023.133549

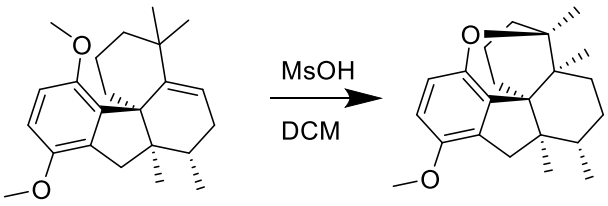
3.2.10



Note: Ag^+ from AgOTf removes Cl^-, driving the reaction toward product formation.

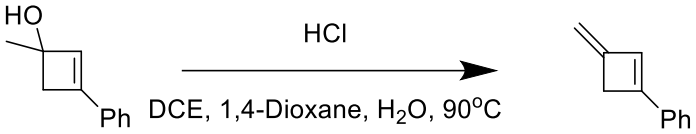
Lei, S.; Bu, S.; Yao, M.; Wang, S. R. Divergent Aromatization of α-Halobenzyl γ-Butenolides Initiated by Selective Enol Protonation to Benzo[c]fluorenones and Naphthalenes. *J. Org. Chem.* 2024, *89* (15), 11067–11071. https://doi.org/10.1021/acs.joc.4c01181.

3.2.11



Chong, C.; Chang, L.; Grimm, I.; Zhang, Q.; Kuang, Y.; Wang, B.; Kang, J.; Liu, W.; Baars, J.; Guo, Y.; Schmalz, H.-G.; Lu, Z. Divergent Total Synthesis of the Revised Structures of Marine Anti-Cancer Meroterpenoids (+)-Dysiherbols A-E. *Chem. Sci.* 2023, *14* (12), 3302-3310. https://doi.org/10.1039/D3SC00173C

3.2.12



Liu, Y.-K.; Yang, P.; Yang, H.; Zhang, J.; Wu, X.-F. Controlled Precursor Differentiation Enables Palladium-Catalyzed Divergent Carbonylation of Cyclobutenols. *J. Am. Chem. Soc.* 2026, *148* (29), 31546-31558. https://doi.org/10.1021/jacs.6c11571

Section 4a: Alkenes 1

Required foundation for this section:

Electrophilic additions

HX addition

X_2 addition

Halohydrin formation

Acid-catalyzed hydration

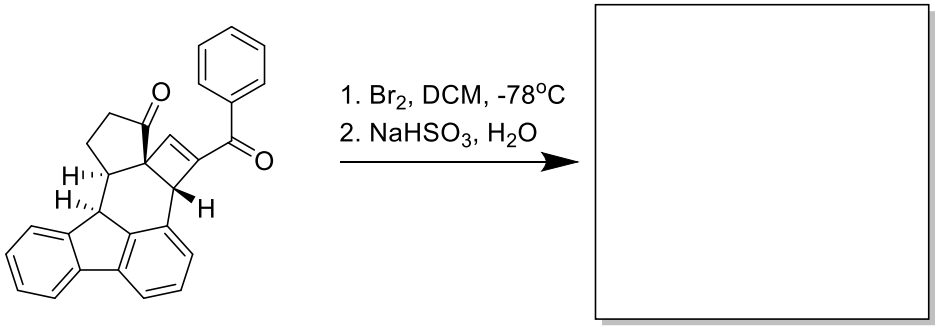
Oxymercuration-demercuration

For section 4a and 4b, it is helpful to remember that alkenes in conjugation with carbonyls (O=C-C=C) may not react like typical alkenes since they have a bit more stability.

Section 4a – Box-Type Questions

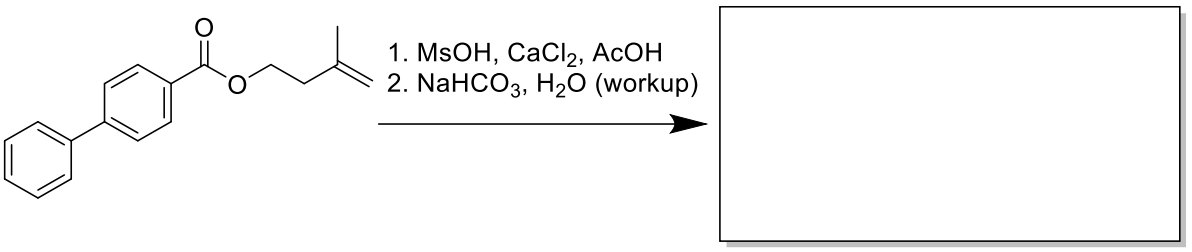
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

4a.1.1



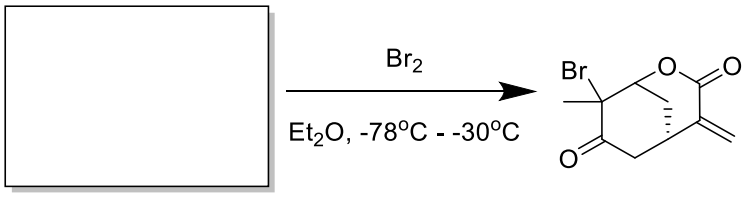
Corti, V.; Barløse, C. L.; Østergaard, N. L.; Kristensen, A.; Jessen, N. I.; Jørgensen, K. A. Organocatalytic Enantioselective Thermal [4 + 4] Cycloadditions. *J. Am. Chem. Soc.* 2023, *145* (2), 1448–1459. https://doi.org/10.1021/jacs.2c12750

4a.1.2



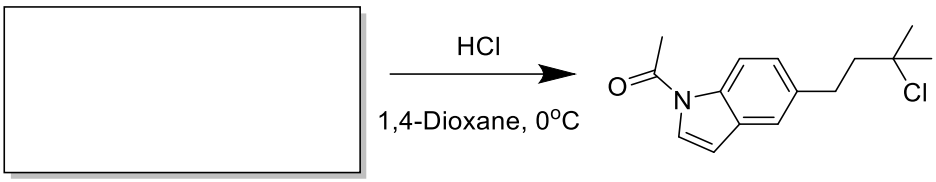
Bertrand, X.; Paquin, P.; Chabaud, L.; Paquin, J.-F. Hydrohalogenation of Unactivated Alkenes Using a Methanesulfonic Acid/Halide Salt Combination. *Synthesis* 2022, *54* (05), 1413–1421. https://doi.org/10.1055/s-0040-1719856

4a.1.3



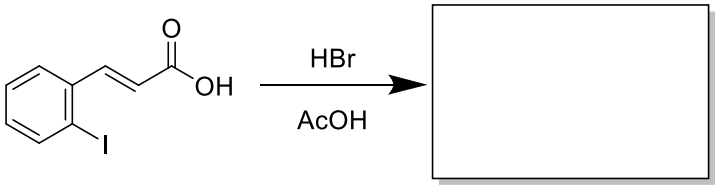
Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* 2024, *26* (22), 4648–4653. https://doi.org/10.1021/acs.orglett.4c01374

4a.1.4



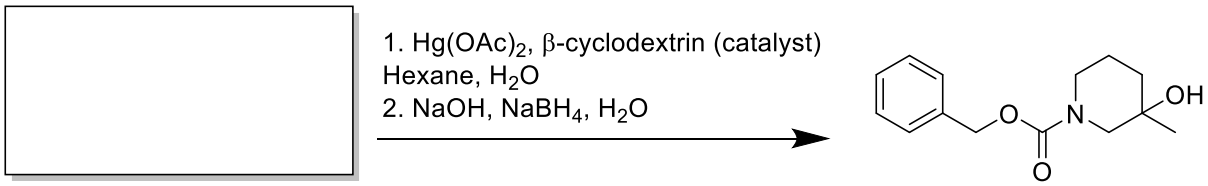
Devarajappa, R.; Hanessian, S. Total Synthesis of Asperdinones B, C, D, E and Terezine D. *Beilstein J. Org. Chem.* 2025, *21*, 2730–2738. https://doi.org/10.3762/bjoc.21.210

4a.1.5



Liu, S.; Díaz-Fernández, M.; Zhang, M.; Huang, F.; Chen, Y.; Yang, Y.; Marín-Beloqui, J. M.; Lan, J.; You, J.; Casado, J.; Zhang, C. Azuperylene: The Nonalternant Isomer of Perylene. *Angew. Chem. Int. Ed.* 2025, *64* (29), e202505897. https://doi.org/10.1002/anie.202505897

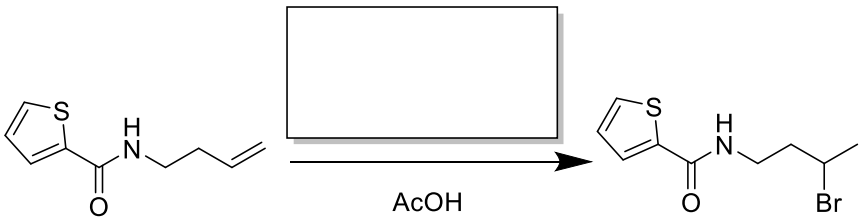
4a.1.6



Note: You can ignore the use of β-cyclodextrin.

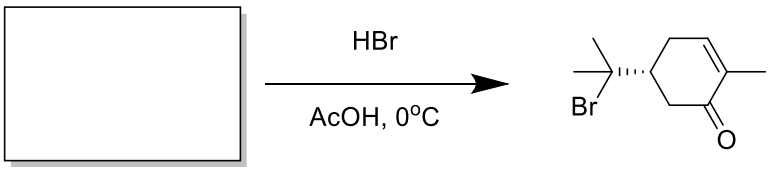
Abreu, A. R.; Costa, I.; Rosa, C.; Ferreira, L. M.; Lourenço, A.; Santos, P. P. New Enantioselective Method for Hydration of Alkenes Using Cyclodextrins as Phase Transfer Catalyst. *Tetrahedron* 2005, *61* (50), 11986–11990. https://doi.org/10.1016/j.tet.2005.09.064

4a.1.7



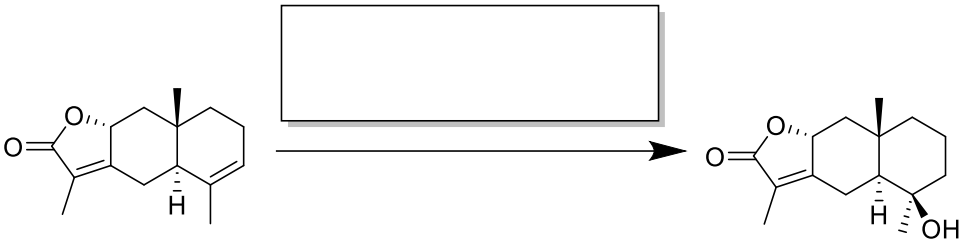
Zi, Q.; Min, L.; Du, H.; Yu, Q.; Li, Y.; Shu, W. Switchable Regiodivergent Reductive Alkyl–Alkyl Coupling by Nickel Catalysis: Sorting Different Alkyl–Nickel Intermediates. *Angew. Chem. Int. Ed.* 2025, *64* (30), e202507313. https://doi.org/10.1002/anie.202507313

4a.1.8



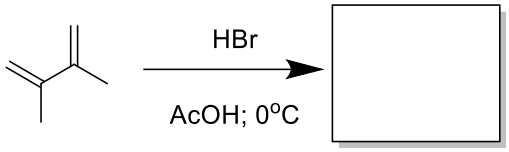
Mori, K. Absolute Configuration of Gomadalactones A, B and C, the Components of the Contact Sex Pheromone of *Anoplophora malasiaca*. *Tetrahedron Lett. 2007*, 48 (32), 5609–5611. https://doi.org/10.1016/j.tetlet.2007.06.054

4a.1.9



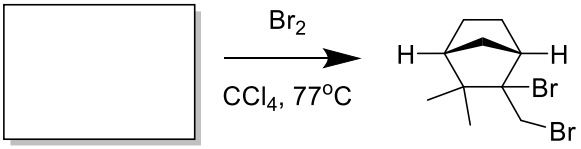
Sreelekshmi, S.; Kaliappan, K. P. A Unified Strategy to the Enantiomers of Atractylenolides and Related Eudesmane Sesquiterpenoids from (−)-Verbenone. *Org. Biomol. Chem.* 2026, *24* (32), 6564–6570. https://doi.org/10.1039/D6OB01041E

4a.1.10



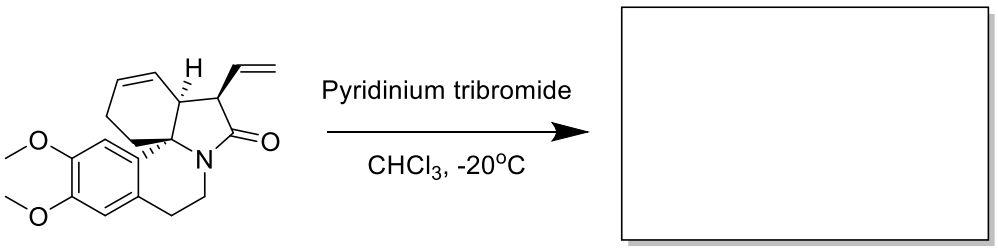
Lavernhe, R.; Wang, Q.; Zhu, J. [4+1] Heteroannulation to Form 1-Pyrrolines through Alder-Ene Reaction of in Situ Generated Ynimines: Development and Application in Total Synthesis of Borrecapine. *Angew. Chem. Int. Ed.* 2025, *64* (2), e202414612. https://doi.org/10.1002/anie.202414612

4a.1.11



Yılmaz, R. F.; Tutar, A.; Islam, M. Z.; Derin, Y.; Ökten, S.; Şahin, E.; Dastan, A. Photo-Induced Bromination of (+)-Camphene and Efficient Synthesis of Novel Camphene-Based Compounds. *SSRN* 2025. https://doi.org/10.2139/ssrn.5166613

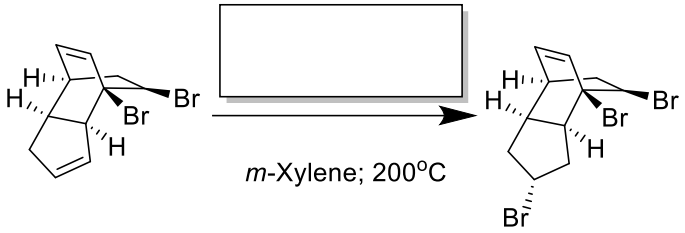
4a.1.12



Note: Pyridinium tribromide is a source for molecular bromine.

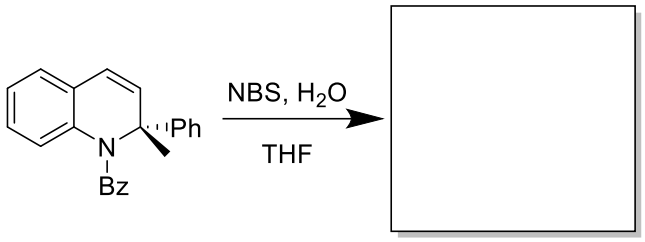
Zhang, F.; Simpkins, N. S.; Blake, A. J. New Approaches for the Synthesis of Erythrinan Alkaloids. *Org. Biomol. Chem.* 2009, *7* (9), 1963-1979. https://doi.org/10.1039/b900189a

4a.1.13



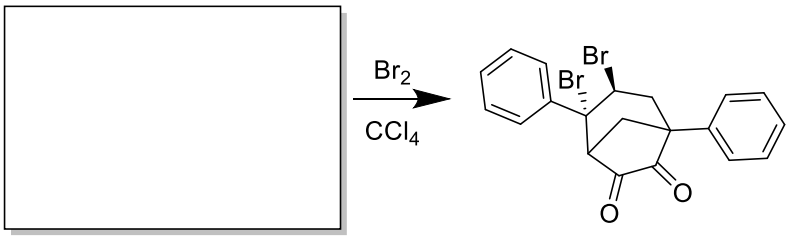
Su, K.-J.; Mieusset, J.-L.; Arion, V. B.; Brecker, L.; Brinker, U. H. Cope Rearrangement versus a Novel Tandem Retro-Diels−Alder−Diels−Alder Reaction with Role Reversal. *Org. Lett.* 2007, *9* (1), 113–115. https://doi.org/10.1021/ol0626793

4a.1.14



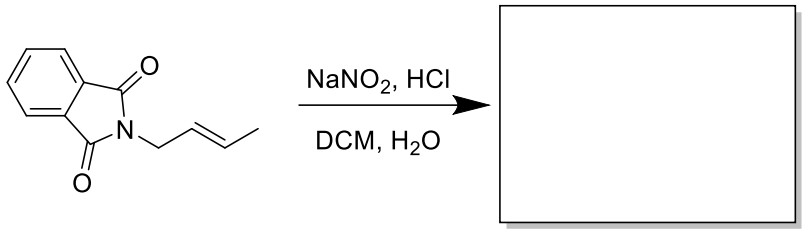
Huang, W.-J.; Chen, J.; Bai, Y.-Q.; Zhou, Y.-G.; Jiang, G.-F.; Wu, B. Asymmetric Synthesis of 2,2-Disubstituted Dihydroquinolines via Rhodium-Catalyzed Dearomative Arylation and Alkenylation of 2-Substituted Quinolinium Salts. *Org. Lett.* 2026, *28* (7), 2284–2288. https://doi.org/10.1021/acs.orglett.5c05303

4a.1.15



Liu, H.; Ji, D.-W.; Min, X.-T.; Mei, Y.-K.; Sun, S.-H.; Zhang, G.; Hu, Y.-C.; Chen, Q.-A. Disproportionation-Inspired Construction of Highly Functionalized Bicyclo[3.2.1]Octanes. *Org. Lett.* 2023, *25* (11), 1878–1882. https://doi.org/10.1021/acs.orglett.3c00397

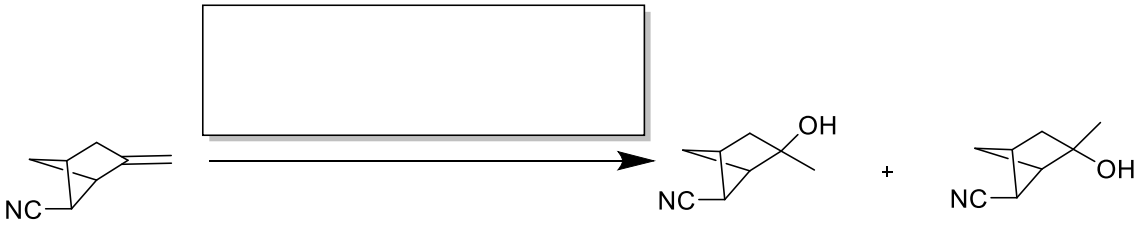
4a.1.16



Note: NO_2^- oxidizes Cl^- to yield molecular chlorine (Cl_2).

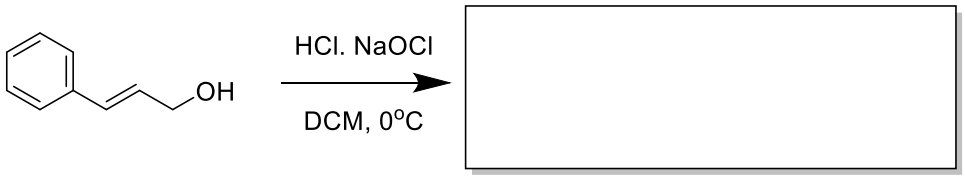
Nong, J.; Cao, Z.; He, Q.; Zhang, Y.; Chen, J.; Wang, Y. A Versatile, Tunable Method for $NaNO_2$ /HX (Cl or Br)-Mediated Radical Dihalogenation or Nitration of Olefins. *Green Chem.* 2025, *27* (46), 14883–14898. https://doi.org/10.1039/D5GC04596G

4a.1.17



Mehta, G.; Singh, S. R.; Balanarayan, P.; Gadre, S. R. Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]Hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects. *Org. Lett.* 2002, *4* (14), 2297–2300. https://doi.org/10.1021/ol026005d

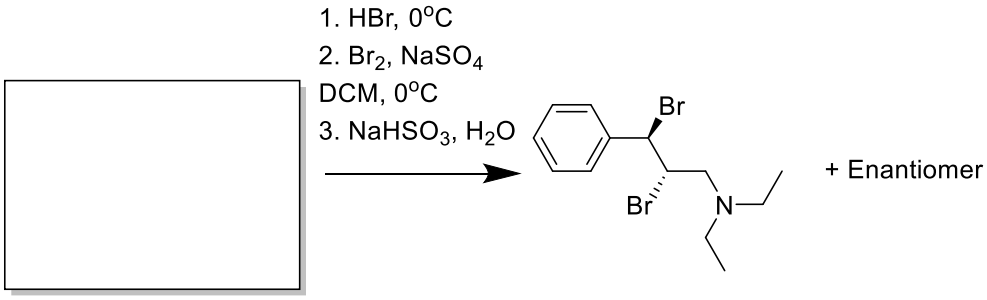
4a.1.18



Note: OCl^- oxidizes Cl^- to yield molecular chlorine.

Aguilar, G. C.; Lis, P. A.; Wise, D. E.; Martinez, J. S.; Parasram, M. Safe and Practical Ex-Situ Chlorination of Electronically Diverse π-Systems. *Tetrahedron Lett.* 2023, *124*, 154591. https://doi.org/10.1016/j.tetlet.2023.154591

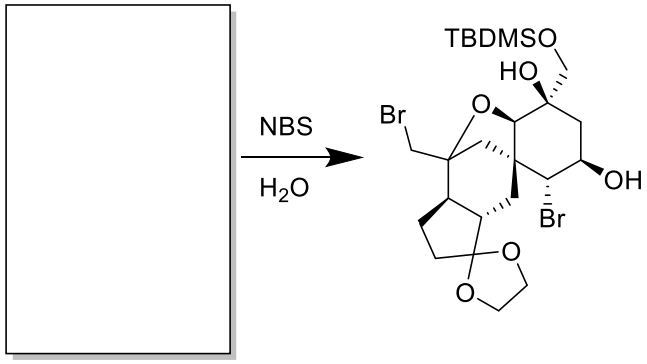
4a.1.19



Note: HBr hinders a certain atom's nucleophilicity.

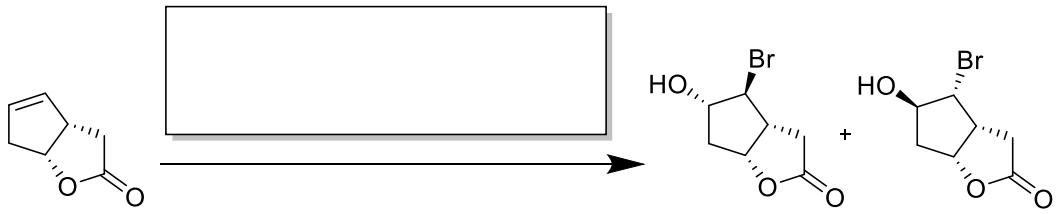
Ahrens, S.; Kusy, R.; Spannenberg, A.; Vuong, T. H.; Rabeah, J.; Russbueldt, B. M. E.; Panten, J.; Jiao, H.; Junge, K.; Beller, M. Cobalt(0)-Catalyzed Isomerization of Allylamines Promoted by Monodentate Benzofuran Phosphines. *J. Am. Chem. Soc.* 2025, *147* (35), 31859–31870. https://doi.org/10.1021/jacs.5c09017

4a.1.20



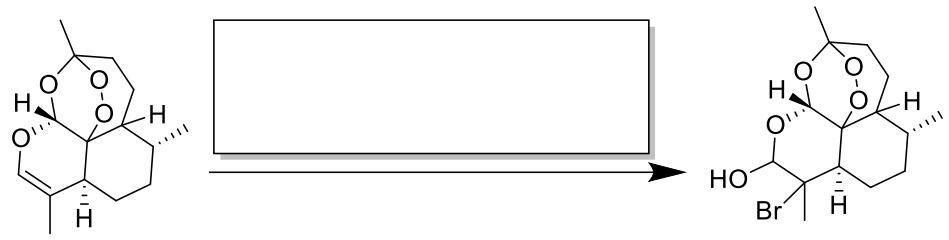
Zhang, Y.; Milkovits, A.; Agarawal, V.; Taylor, C. A.; Snyder, S. A. Total Synthesis of the Meroterpenoid Manginoid A as Fueled by a Challenging Pinacol Coupling and Bicycle-forming Etherification. *Angew. Chem. Int. Ed.* 2021, *60* (20), 11127–11132. https://doi.org/10.1002/anie.202016178

4a.1.21



Yin, Y.; Wang, J.; Li, J. A Concise and Scalable Chemoenzymatic Synthesis of Prostaglandins. *Nat. Commun.* 2024, *15* (1), 2523. https://doi.org/10.1038/s41467-024-46960-y

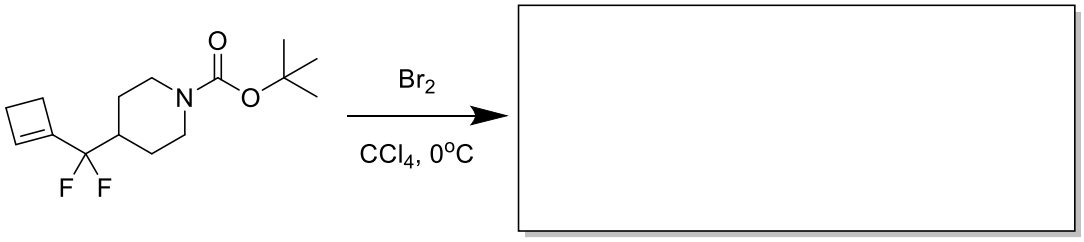
4a.1.22



Note: $NaHSO_3$ quenches excess bromine.

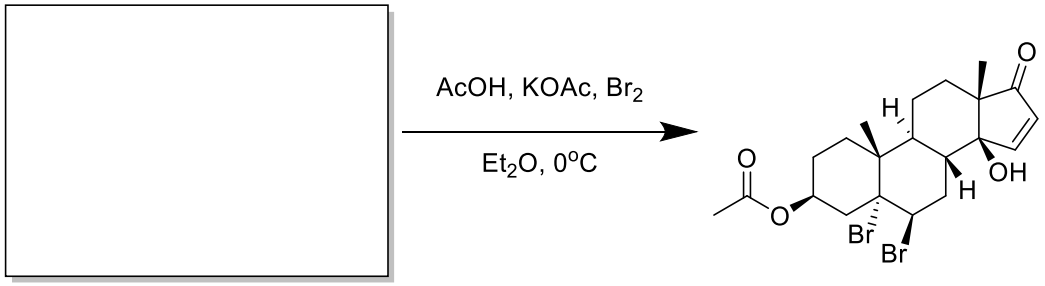
Qing, L.; Yu, Q.; Wang, C.; Lu, X.; Yang, Y.; Chen, X.; Li, X.; Min, J.; Pan, W.; He, H.; Zhong, H.; Zhang, S. Discovery of D-Ring-Contracted Artemisinin as a Potent Hydrophobic Tag for Targeted Protein Degradation. *J. Med. Chem.* 2025, *68* (2), 1619–1631. https://doi.org/10.1021/acs.jmedchem.4c02269

4a.1.23



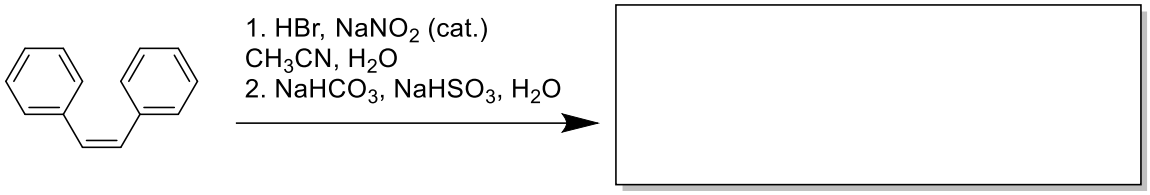
Feng, X.-T.; Min, Q.-Q.; Zhang, S.-Y.; Zhao, H.-Y.; Zhang, X. Difluoromethylene Cyclobutyl Sulfonium Salts: Versatile Reagents for Chemodivergent Synthesis of Difluoroalkylated Cyclobutenes and Cyclobutanes. *Chem. Sci.* 2025, *16* (36), 16552–16558. https://doi.org/10.1039/D5SC05409E

4a.1.24



Mi, Y.; Ren, Y.-H.; Li, Y.; Zhang, R.-C.; Zhao, J.-X.; Zhou, B.; Yue, J.-M. Rare Chlorinated C_{19} Steroids Hocarnoids A and B from *Hoya Carnosa* : Isolation, Semisynthesis, and Anti-Inflammation. *J. Org. Chem.* 2025, *90* (13), 4714–4724. https://doi.org/10.1021/acs.joc.5c00211

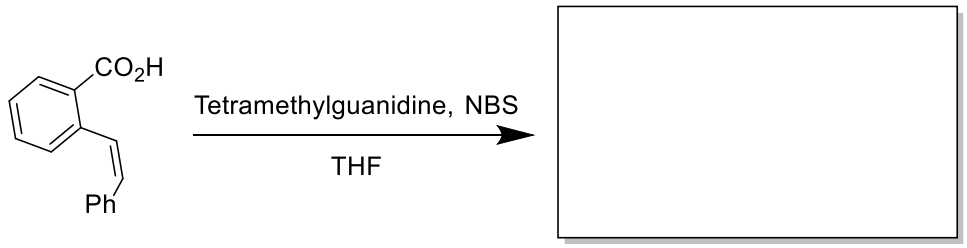
4a.1.25



Note: NO_2^- oxidizes Br^- to yield molecular bromine (Br_2).

Podgoršek, A.; Eissen, M.; Fleckenstein, J.; Stavber, S.; Zupan, M.; Iskra, J. Selective Aerobic Oxidative Dibromination of Alkenes with Aqueous HBr and Sodium Nitrite as a Catalyst. *Green Chem.* 2009, *11* (1), 120–126. https://doi.org/10.1039/B814989E

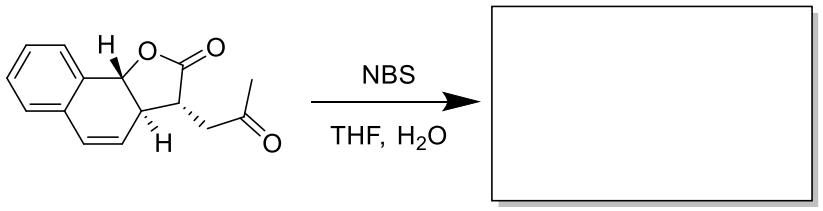
4a.1.26



Note: Tetramethylguanidine is a base

Sugano, M.; Fujiwara, T.; Mochizuki, W.; Inokuma, T.; Yamada, K. Catalyst-Controlled Regioselectivity Switching Inthe Bromolactonization of (*Z*)-StilbenecarboxylicAcids. *Org. Lett.* 2026, *28* (28), 8872–8877. https://doi.org/10.1021/acs.orglett.6c02195

4a.1.27



Hint: NBS provides an electrophilic bromine.

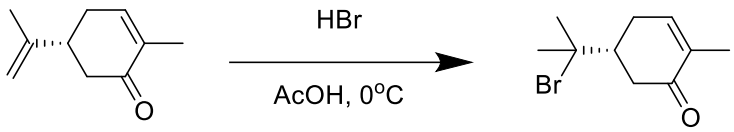
Gan, L.; Li, Z.Q.; Chen, T.; Wan, X.; Zhang, J.; Ren, J.; Jiang, M.; Cao, P.; Huang, J.; Deng, Y.H.; Peng, F.; Tian, R.; Wang, Y.; Zhang, Z.; Shao, Z. Highly Cα-Regio-, Enantio- and Diastereoselective

Mukaiyama-Type Annulation of Siloxyfurans: Stereodivergent Synthesis of Multi-Stereogenic Tricyclic γ-Lactones. *Chem. Sci*. 2026, *17* (23), 11445-11458. https://doi.org/10.1039/d6sc01491g

Section 4a – Mechanism Questions

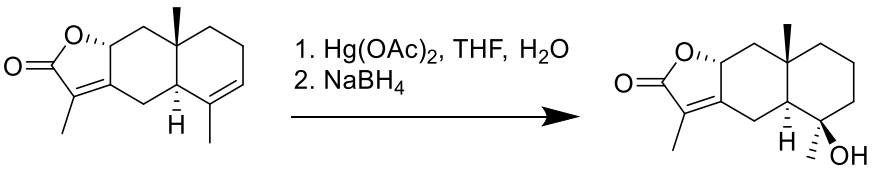
Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

4a.2.1



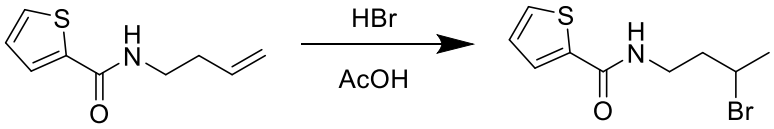
Mori, K. Absolute Configuration of Gomadalactones A, B and C, the Components of the Contact Sex Pheromone of *Anoplophora malasiaca*. *Tetrahedron Lett. 2007*, 48 (32), 5609–5611. https://doi.org/10.1016/j.tetlet.2007.06.054

4a.2.2



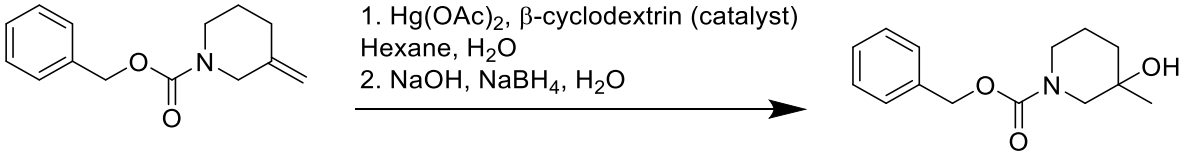
Sreelekshmi, S.; Kaliappan, K. P. A Unified Strategy to the Enantiomers of Atractylenolides and Related Eudesmane Sesquiterpenoids from (−)-Verbenone. *Org. Biomol. Chem.* 2026, *24* (32), 6564–6570. https://doi.org/10.1039/D6OB01041E

4a.2.3



Zi, Q.; Min, L.; Du, H.; Yu, Q.; Li, Y.; Shu, W. Switchable Regiodivergent Reductive Alkyl–Alkyl Coupling by Nickel Catalysis: Sorting Different Alkyl–Nickel Intermediates. *Angew. Chem. Int. Ed.* 2025, *64* (30), e202507313. https://doi.org/10.1002/anie.202507313

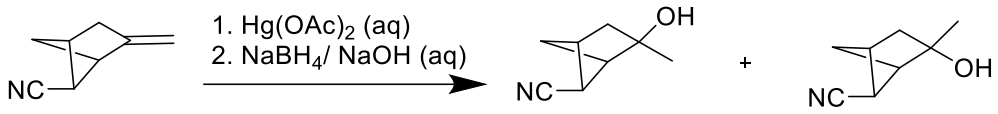
4a.2.4



Note: You can ignore β-cyclodextrin when drawing the reaction mechanism.

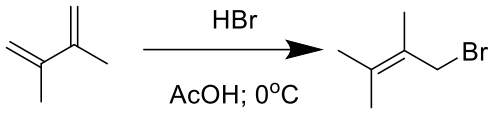
Abreu, A. R.; Costa, I.; Rosa, C.; Ferreira, L. M.; Lourenço, A.; Santos, P. P. New Enantioselective Method for Hydration of Alkenes Using Cyclodextrins as Phase Transfer Catalyst. *Tetrahedron* 2005, *61* (50), 11986–11990. https://doi.org/10.1016/j.tet.2005.09.064

4a.2.5



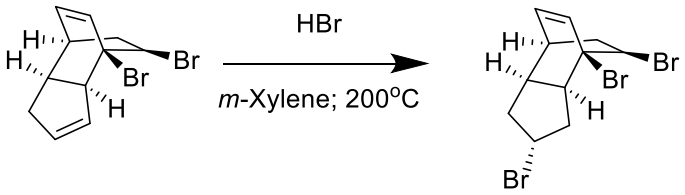
Mehta, G.; Singh, S. R.; Balanarayan, P.; Gadre, S. R. Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]Hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects. *Org. Lett.* 2002, *4* (14), 2297–2300. https://doi.org/10.1021/ol026005d

4a.2.6



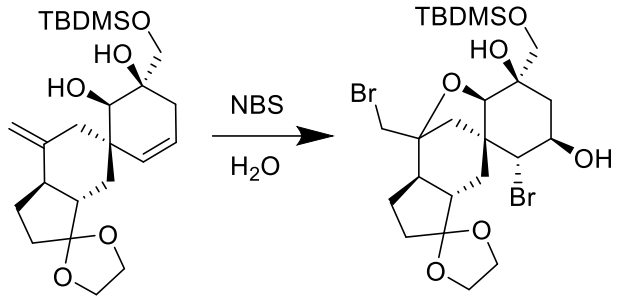
Lavernhe, R.; Wang, Q.; Zhu, J. [4+1] Heteroannulation to Form 1-Pyrrolines through Alder-Ene Reaction of in Situ Generated Ynimines: Development and Application in Total Synthesis of Borrecapine. *Angew. Chem. Int. Ed.* 2025, *64* (2), e202414612. https://doi.org/10.1002/anie.202414612

4a.2.7



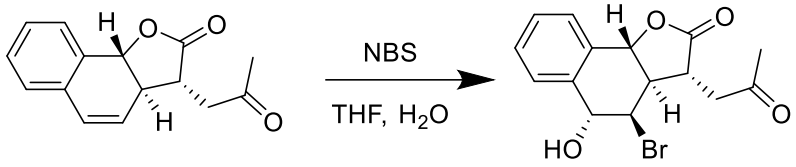
Su, K.-J.; Mieusset, J.-L.; Arion, V. B.; Brecker, L.; Brinker, U. H. Cope Rearrangement versus a Novel Tandem Retro-Diels−Alder−Diels−Alder Reaction with Role Reversal. *Org. Lett.* 2007, *9* (1), 113–115. https://doi.org/10.1021/ol0626793

4a.2.8



Zhang, Y.; Milkovits, A.; Agarawal, V.; Taylor, C. A.; Snyder, S. A. Total Synthesis of the Meroterpenoid Manginoid A as Fueled by a Challenging Pinacol Coupling and Bicycle-forming Etherification. *Angew. Chem. Int. Ed.* 2021, *60* (20), 11127–11132. https://doi.org/10.1002/anie.202016178

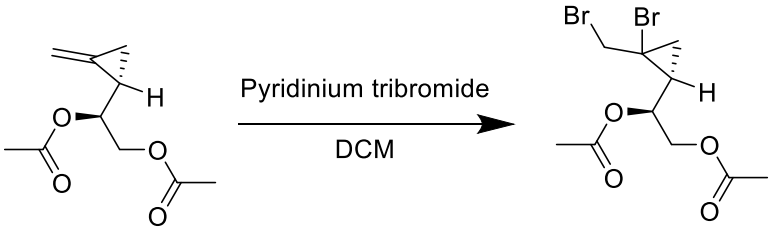
4a.2.9



Hint: NBS provides an electrophilic bromine.

Gan, L.; Li, Z.Q.; Chen, T.; Wan, X.; Zhang, J.; Ren, J.; Jiang, M.; Cao, P.; Huang, J.; Deng, Y.H.; Peng, F.; Tian, R.; Wang, Y.; Zhang, Z.; Shao, Z. Highly Cα-Regio-, Enantio- and Diastereoselective Mukaiyama-Type Annulation of Siloxyfurans: Stereodivergent Synthesis of Multi-Stereogenic Tricyclic γ-Lactones. *Chem. Sci*. 2026, *17* (23), 11445-11458. https://doi.org/10.1039/d6sc01491g

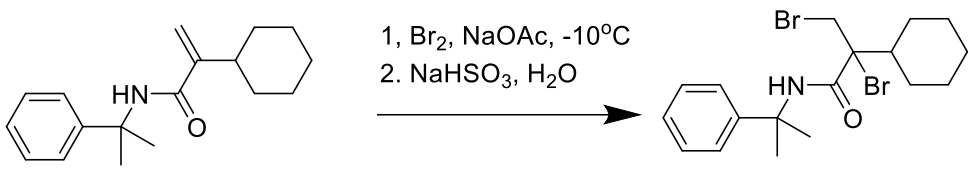
4a.2.10



Note: Pyridinium tribromide is a source for molecular bromine.

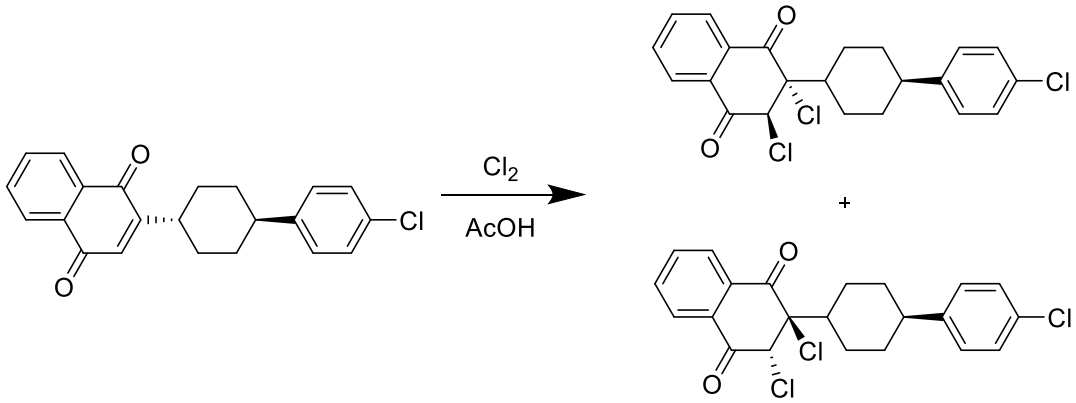
Zhou, S.; Drach, J. C.; Prichard, M. N.; Zemlicka, J. (*Z*)- and (*E*)-2-(1,2-Dihydroxyethyl)Methylenecyclopropane Analogues of 2′-Deoxyadenosine and 2′-Deoxyguanosine. Synthesis of All Stereoisomers, Absolute Configuration, and Antiviral Activity. *J. Med. Chem.* 2009, *52* (10), 3397–3407. https://doi.org/10.1021/jm900126v

4a.2.11



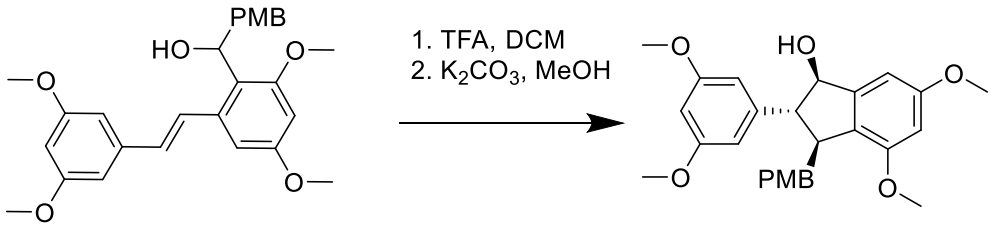
Gao, D.; Qin, L.-Z.; Li, Z.-L.; Gu, Q.-S.; Liu, X.-Y. Copper-Catalysed Enantioconvergent Radical C(Sp3)–C(Sp3) Cross-Coupling of Tertiary Electrophiles with Cyclopropanols for Quaternary Carbon Formation. *Nat. Synth* 2026, *5* (5), 750–760. https://doi.org/10.1038/s44160-025-00987-1

4a.2.12



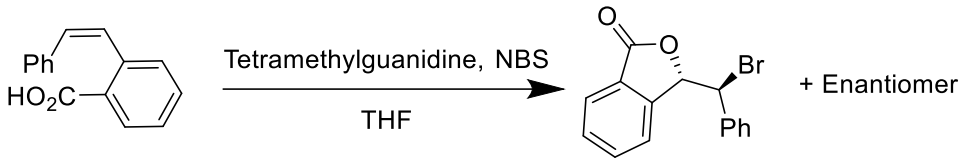
Dike, S. Y.; Singh, D.; Thankachen, B. N.; Sharma, B.; Mathur, P. K.; Kore, S.; Kumar, A. A Single-Pot Synthesis of Atovaquone: An Antiparasitic Drug of Choice. *Org. Process Res. Dev.* 2014, *18* (5), 618–625. https://doi.org/10.1021/op500032w

4a.2.13



Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. Total Synthesis of Diverse Carbogenic Complexity within the Resveratrol Class from a Common Building Block. *J. Am. Chem. Soc.* 2009, *131* (5), 1753–1765. https://doi.org/10.1021/ja806183r

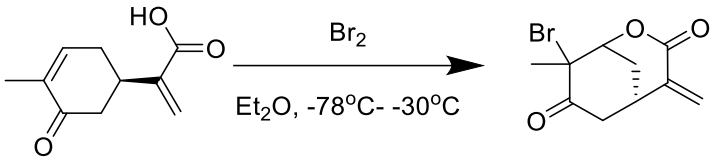
4a.2.14



Note: Tetramethylguanidine is a base. For the reaction mechanism, you can represent this structure as NR_3.

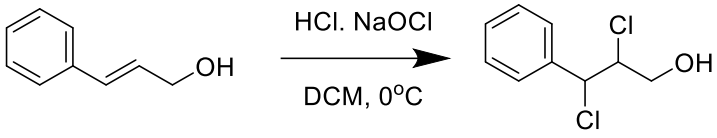
Sugano, M.; Fujiwara, T.; Mochizuki, W.; Inokuma, T.; Yamada, K. Catalyst-Controlled Regioselectivity Switching Inthe Bromolactonization of (*Z*)-Stilbenecarboxylic Acids. *Org. Lett.* 2026, *28* (28), 8872–8877. https://doi.org/10.1021/acs.orglett.6c02195

4a.2.15



Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* 2024, *26* (22), 4648–4653. https://doi.org/10.1021/acs.orglett.4c01374

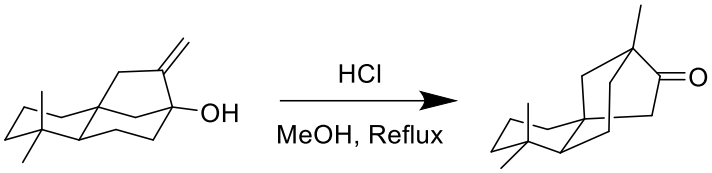
4a.2.16



Hint: OCl^- oxidizes Cl^- to yield molecular chlorine (Cl_2).

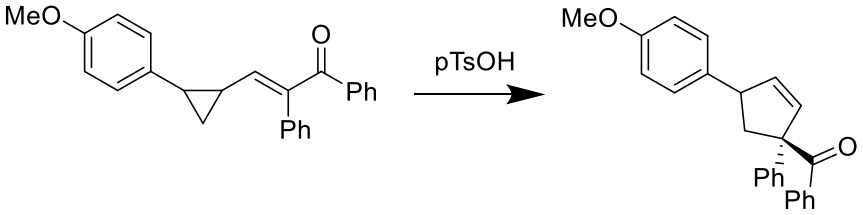
Aguilar, G. C.; Lis, P. A.; Wise, D. E.; Martinez, J. S.; Parasram, M. Safe and Practical Ex-Situ Chlorination of Electronically Diverse π-Systems. *Tetrahedron Lett.* 2023, *124*, 154591. https://doi.org/10.1016/j.tetlet.2023.154591

4a.2.17



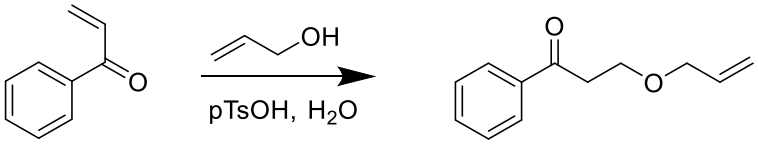
Eggert, A.; Schuppe, K. T.; Fuchs, H. L. S.; Brönstrup, M.; Kalesse, M. Total Synthesis of Acanthodoral Using a Rearrangement Strategy. *Org. Lett*. 2024, *26* (15), 2893–2896. https://doi.org/10.1021/acs.orglett.3c03717

4a.2.18



Laru, C. Rearrangement of Donor-Acceptor Cyclopropanes for the Synthesis of Substituted Cyclopentene Derivatives. *J. Org. Chem.* 2026, *91* (19), 6596-6609. https://doi.org/10.1021/acs.joc.6c00063

4a.2.19



Wang, Y.; Hong, F.; Robertson, C. M.; Mudd, R. J.; Bower, J. F. Iridium-Catalyzed Stereoselective α-Alkylation of α-Hydroxy Ketones with Minimally Polarized Alkenes. *J. Am. Chem. Soc.* 2026, *148* (4), 3911–3917. https://doi.org/10.1021/jacs.5c19724

Section 4b: Alkenes 2

Required foundation for this section:

Electrophilic additions

Hydroboration-oxidation

Catalytic hydrogenation

Epoxidation (mCPBA and intramolecular substitution); acid- and base-catalyzed epoxide opening

Ozonolysis (oxidative and reductive workups)

Dihydroxylation (for syn and anti products)

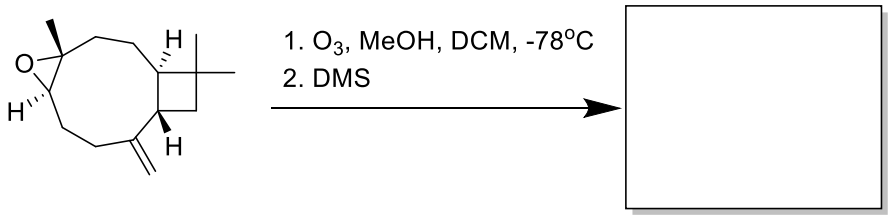
Cleaving dihydroxyl groups

Allylic bromination

Section 4b – Box-Type Questions

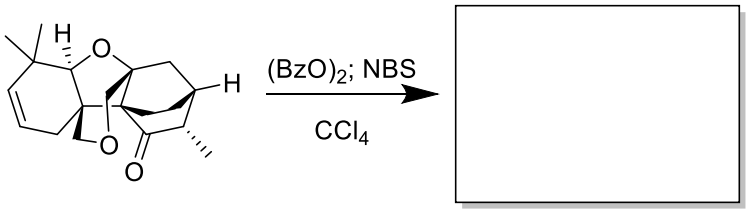
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

4b.1.1



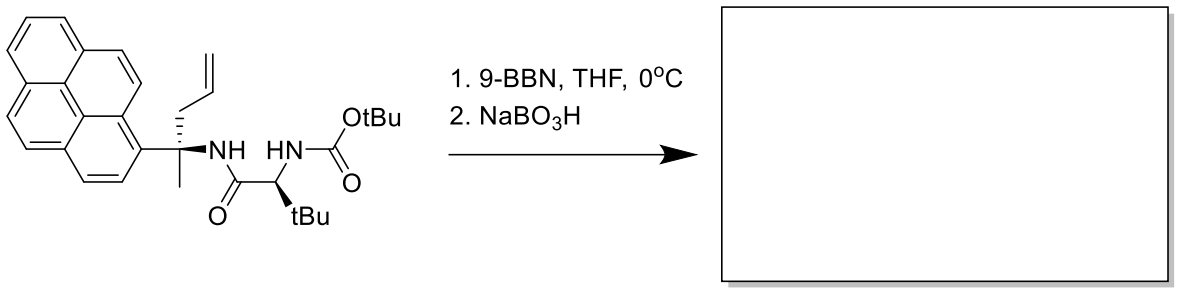
Prout, E. S.; Kwon, O.; Silva, T. G. Regioselective Synthesis of Methyl Enol Ethers from Cycloalkanones via O-Methylation of Kinetic Enolates. *Synthesis* 2026, *58* (13), 1527–1538. https://doi.org/10.1055/a-2822-8676

4b.1.2



Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. Enantioselective Total Synthesis of (−)-Maoecrystal V. *J. Am. Chem. Soc.* 2014, *136* (51), 17750–17756. https://doi.org/10.1021/ja5109694

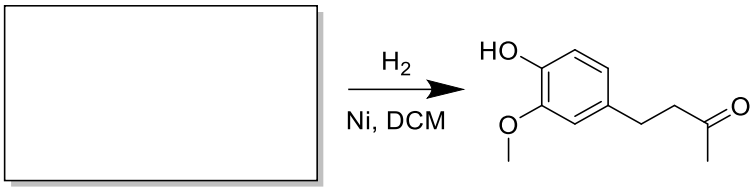
4b.1.3



Note: $NaBO_3H$ (sodium peroxoborate) is O=B-O-O-H (analogous to using $NaOH+H_2O_2$)

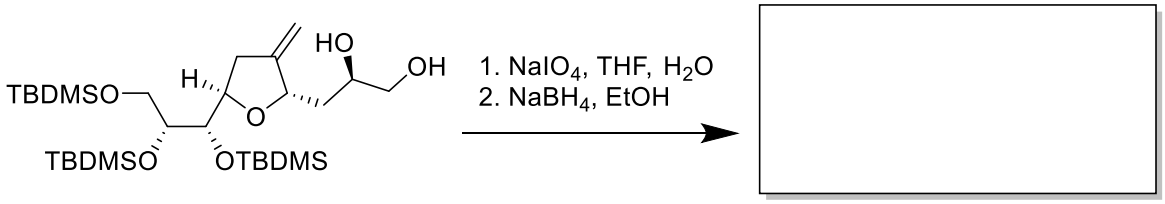
Adrianov, T.; Jacobsen, E. N. Chiral Hydrogen-Bond Donor and Gold(I) Cocatalysis Enables Enantioselective Dearomative Spirocyclization of Naphthols. *J. Am. Chem. Soc.* 2025, *147* (45), 41229–41236. https://doi.org/10.1021/jacs.5c15891

4b.1.4



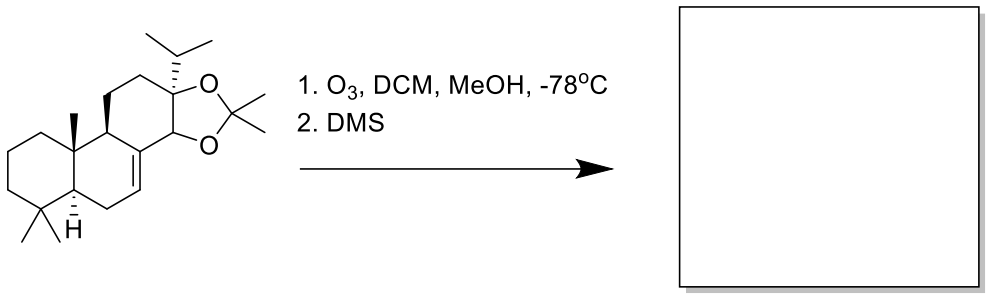
Zhang, Y.; Fayad, E.; Katouah, H. A.; Qin, H.-L. Solvent-Controlled and Highly Chemoselective Reduction of α,β-Unsaturated Ketones and Aldehydes. *J. Org. Chem.* 2025, *90* (16), 5704–5709. https://doi.org/10.1021/acs.joc.5c00151

4b.1.5



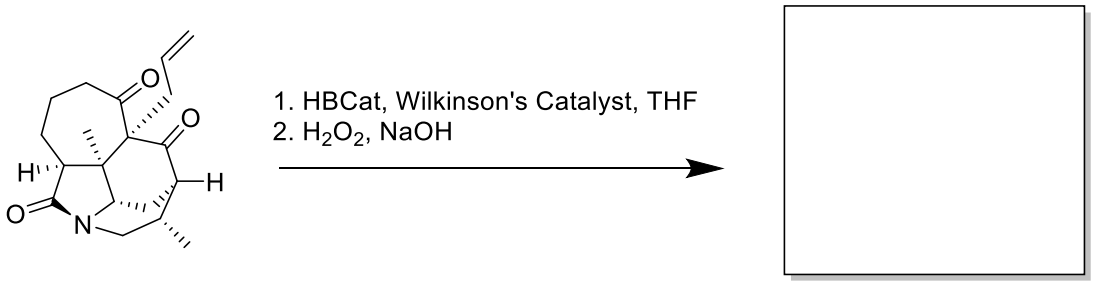
Romiti, F.; Decultot, L.; Clark, J. S. Convergent Synthesis of the C1–C29 Framework of Amphidinolide F. *J. Org. Chem.* 2022, *87* (12), 8126–8141. https://doi.org/10.1021/acs.joc.2c00850

4b.1.6



Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. Enantioselective Total Synthesis of Cytotoxic Taiwaniaquinones A and F. *Chem. Commun.* 2010, *46* (48), 9244. https://doi.org/10.1039/c0cc03763j

4b.1.7



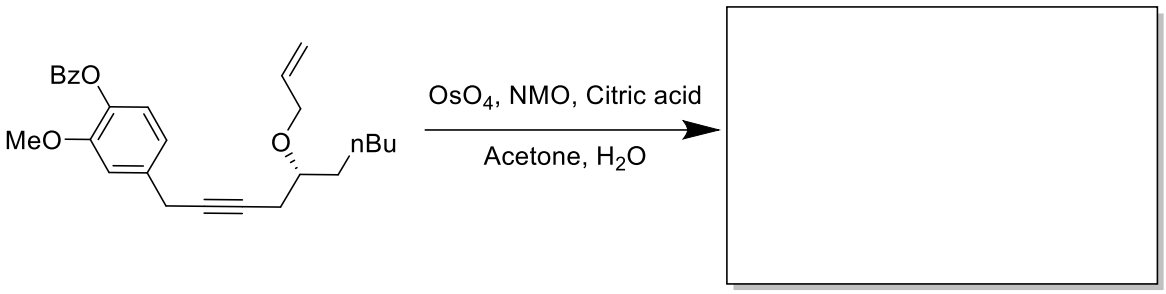
Zhang, Y.; Chen, Y.; Xu, J. Total Synthesis of Daphniphyllum Alkaloids: (+)-Daphlongamine E, (+)-Calyciphylline R, and (–)-10-Deoxydaphnipaxianine A. *Synthesis* 2024, *56* (08), 1273–1284. https://doi.org/10.1055/a-2244-1600

4b.1.8



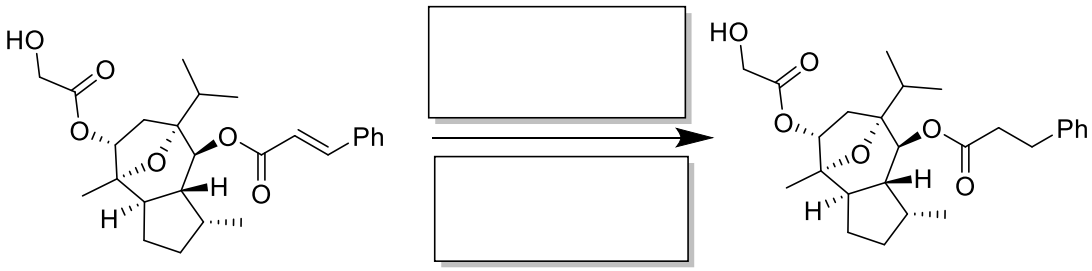
Monerris Mascaro, M.; Henderson, A. P.; Drozdowska, M.; Richardson, R.; Nagel-Savage, D.; Hall, M. J.; Longcake, A.; Mardiana, L.; Golding, B. T. Total Synthesis of 8-Hydroxy-Dihydroergotamine, the Major Human Metabolite of Dihydroergotamine. *Molecules* 2026, *31* (9), 1547. https://doi.org/10.3390/molecules31091547

4b.1.9



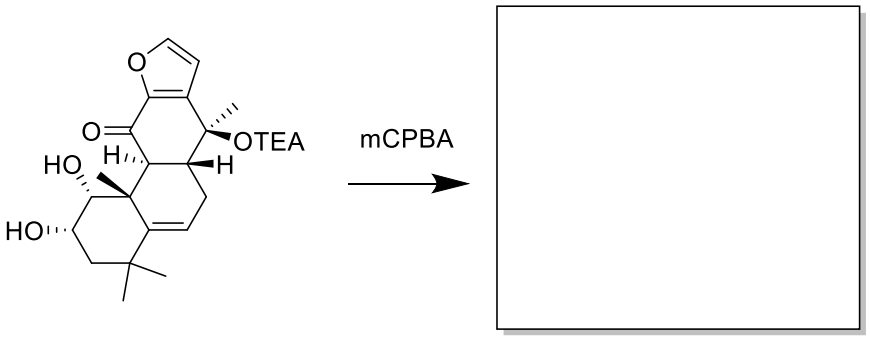
Shet, M. N.; Ramana, C. V. Total Synthesis of (−) and (+)-Zingibergingerols A. *J. Org. Chem.* 2024, *89* (22), 16923–16928. https://doi.org/10.1021/acs.joc.4c01649

4b.1.10



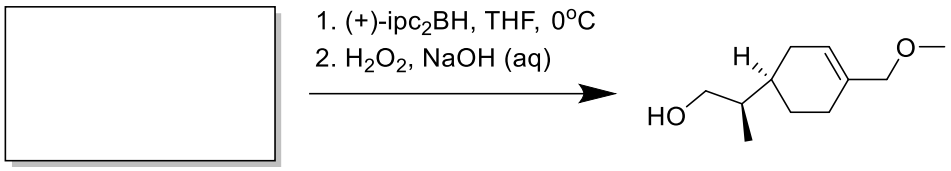
Nicolaou, K. C.; Kang, Q.; Ng, S. Y.; Chen, D. Y.-K. Total Synthesis of Englerin A. *J. Am. Chem. Soc.* 2010, *132* (23), 8219–8222. https://doi.org/10.1021/ja102927n

4b.1.11



Papidocha, S. M.; Bulthaupt, H. H.; Carreira, E. M. Synthesis of Neocaesalpin A, AA, and Nominal Neocaesalpin K**. *Angew. Chem. Int. Ed.* 2023, *62* (48), e202310149. https://doi.org/10.1002/anie.202310149

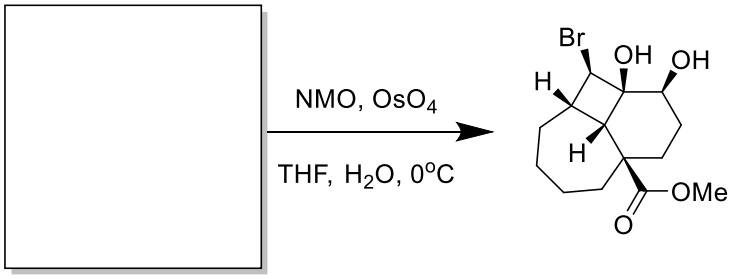
4b.1.12



Note: (+)-ipc$_2$BH (diisopinocampheylborane) is a bulky and chiral hydroboration reagent.

Kuwabara, M.; Matsuo, A.; Kamo, S.; Matsuzawa, A.; Sugita, K. Stereoselective Convergent Synthesis of Carbon Skeleton of Cotylenin A Aglycone. *Synthesis* 2021, *53* (12), 2092–2102. https://doi.org/10.1055/s-0040-1706684

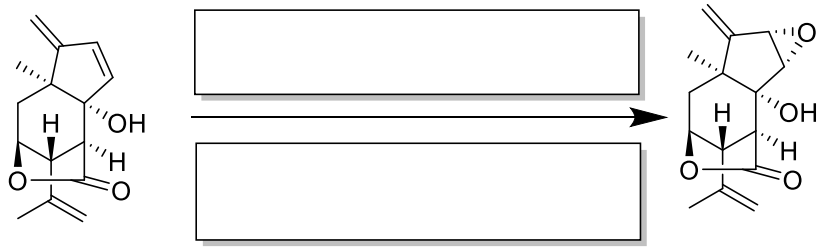
4b.1.13



(Only this stereoisomer is made.)

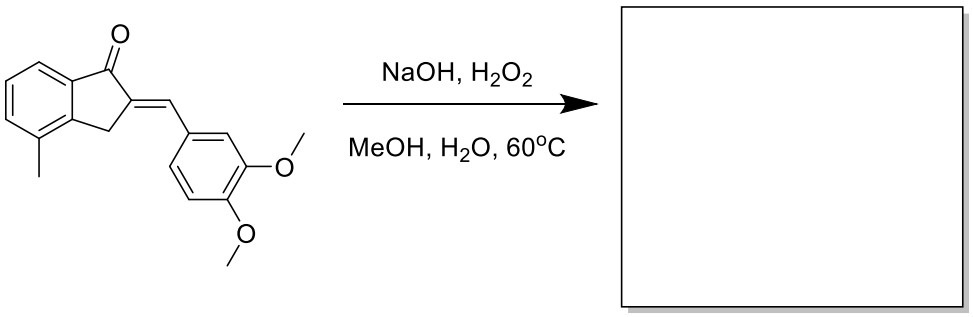
Cao, S.-Y.; Yue, H.-J.; Zhu, M.-Q.; Xu, L. Synthesis of Tricyclo[7.2.1.0^{9,10}]Dodecan-11-One Core Ring Systems of Norditerpenoid Alkaloids and Racemulosine. *Org. Chem. Front.* 2020, *7* (7), 933–937. https://doi.org/10.1039/D0QO00088D

4b.1.14



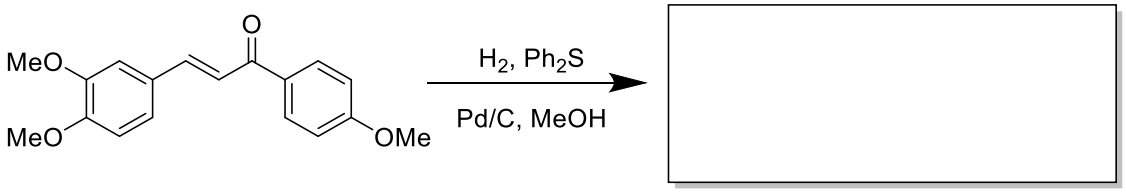
Kuwabara, M.; Matsuo, A.; Kamo, S.; Matsuzawa, A.; Sugita, K. Stereoselective Convergent Synthesis of Carbon Skeleton of Cotylenin A Aglycone. *Synthesis* 2021, *53* (12), 2092–2102. https://doi.org/10.1055/s-0040-1706684

4b.1.15



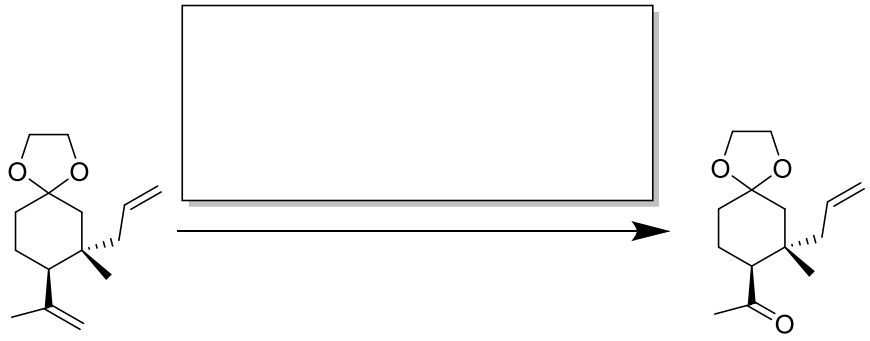
Story, J. B.; Ringler, K. E.; Nguyen, C. L.; Drance, M. J.; Howard, E. M. Synthesis of 2-Naphthols via a Trifluoroacetic Acid-Mediated Epoxy Alcohol Rearrangement. *J. Org. Chem.* 2026, *91* (14), 5249–5254. https://doi.org/10.1021/acs.joc.6c00021

4b.1.16



Deka, U.; Gogoi, A.; Das, S. K. Reactivity Divergence in the Cyclization of Terminal Epoxides All-Carbon-Tethered to Indoles. *Chem. Commun.* 2026, *62* (7), 2222–2225. https://doi.org/10.1039/D5CC06074E

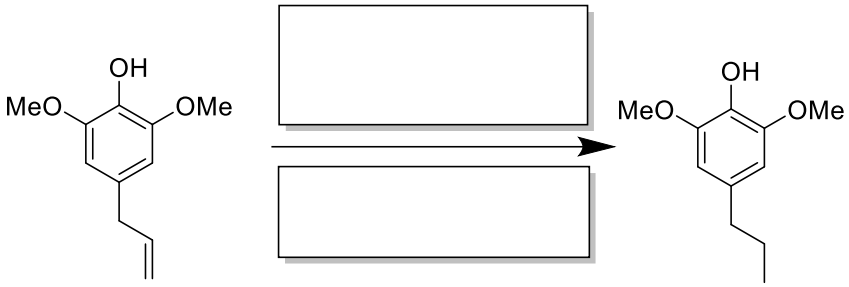
4b.1.17



Note: For introductory organic chemistry courses, you typically do not need to know why this reaction occurred only on the specific functional group.

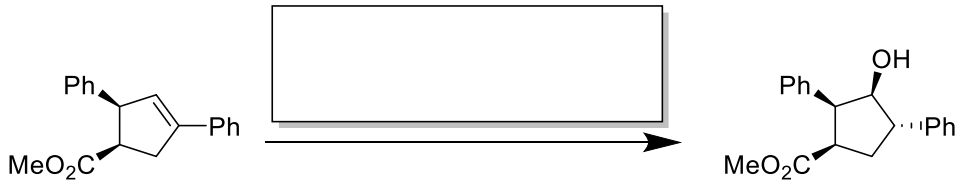
Sreelekshmi, S.; Kaliappan, K. P. A Unified Strategy to the Enantiomers of Atractylenolides and Related Eudesmane Sesquiterpenoids from (−)-Verbenone. *Org. Biomol. Chem.* 2026, *24* (32), 6564–6570. https://doi.org/10.1039/D6OB01041E

4b.1.18



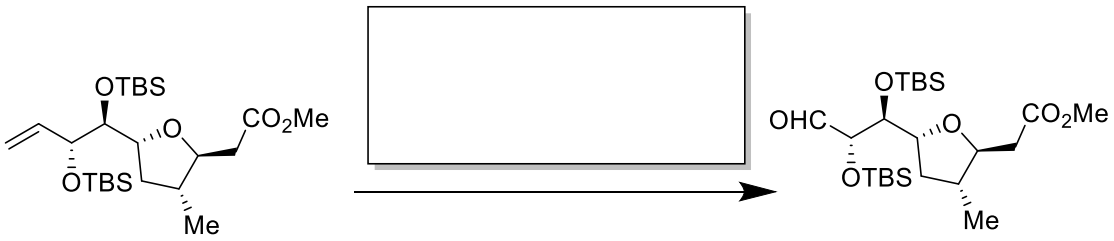
Li, X.; Chavez, A. J.; Zhang, H.; Andryushkina, D.; Ford, P. C.; Abu-Omar, M. M. Selective Conversion of Lignin to Benzoquinones under Ambient Conditions: Unlocking the Potential of a Single Platform Chemical Strategy. *Green Chem.* 2026, *28* (9), 4255–4262. https://doi.org/10.1039/D5GC04121J

4b.1.19



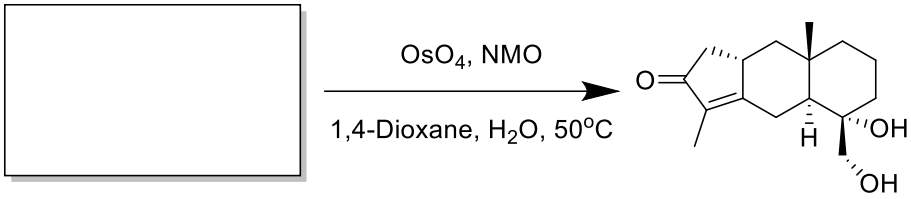
Zhao, J.; He, L.; Lv, H. Enantioselective Synthesis of Chiral Cyclopentenes by Relay Catalysis from Terminal Alkynes, Enones, and Syngas. *Org. Lett.* 2026, *28* (1), 202–207. https://doi.org/10.1021/acs.orglett.5c04598

4b.1.20



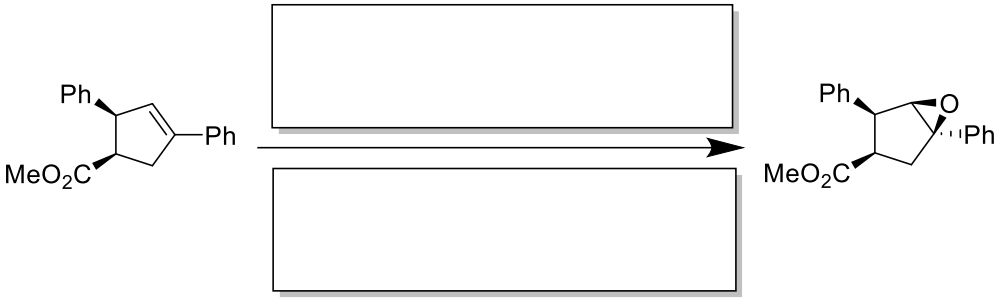
Ciss, I.; Seck, M.; Figadère, B.; Ferrié, L. Advances Toward Amphidinolides C, F and U: Isolations, Synthetic Studies and Total Syntheses. *Chem. Eur. J.* 2024, *30* (27), e202400471. https://doi.org/10.1002/chem.202400471

4b.1.21



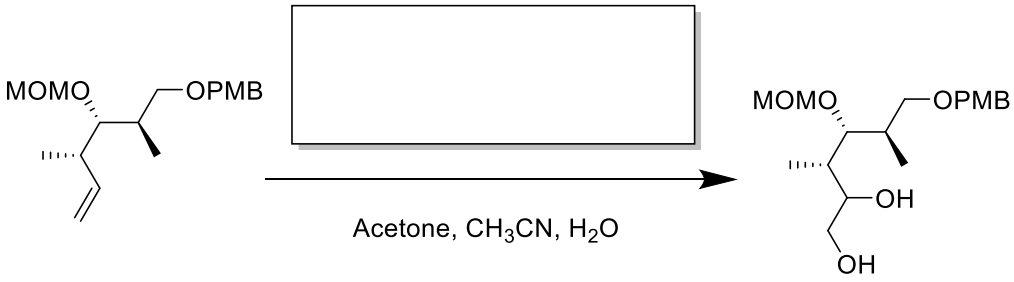
Sreelekshmi, S.; Kaliappan, K. P. A Unified Strategy to the Enantiomers of Atractylenolides and Related Eudesmane Sesquiterpenoids from (−)-Verbenone. *Org. Biomol. Chem.* 2026, *24* (32), 6564–6570. https://doi.org/10.1039/D6OB01041E

4b.1.22



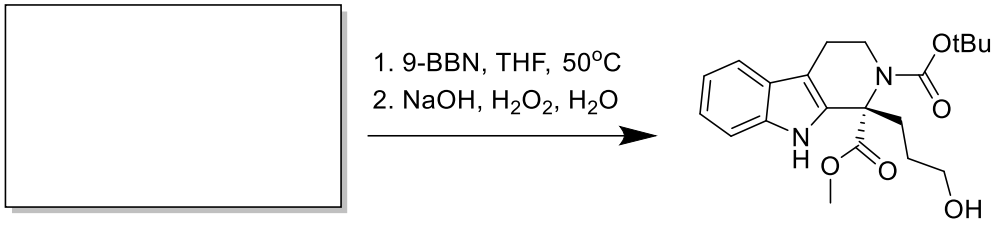
Zhao, J.; He, L.; Lv, H. Enantioselective Synthesis of Chiral Cyclopentenes by Relay Catalysis from Terminal Alkynes, Enones, and Syngas. *Org. Lett.* 2026, *28* (1), 202–207. https://doi.org/10.1021/acs.orglett.5c04598

4b.1.23



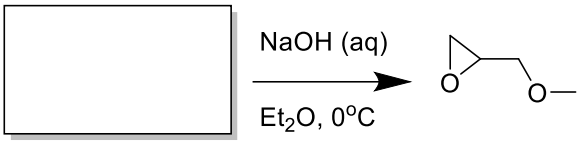
Sennari, G.; Watanabe, A.; Ōno, T.; Oshita, J.; Noguchi, Y.; Hirose, T.; Sunazuka, T. Macrocyclic Skeletal Modification Approach to the Anti-Trypanosomal Macrolides, Actinoallolides. *Chem. Commun.* 2025, *61* (56), 10367–10370. https://doi.org/10.1039/D5CC01915J

4b.1.24



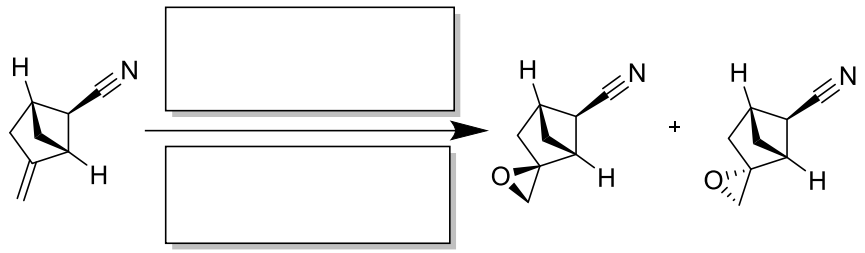
Wang, Z.; Chen, D.; Chang, J.; Li, Y.; Su, Y.; Tang, P.; Chen, F.-E. Enantioselective Synthesis of Functionalized 2,2-Disubstituted Piperidines Enabled by Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation. *Org. Lett.* 2026, *28* (2), 794–799. https://doi.org/10.1021/acs.orglett.5c04932

4b.1.25



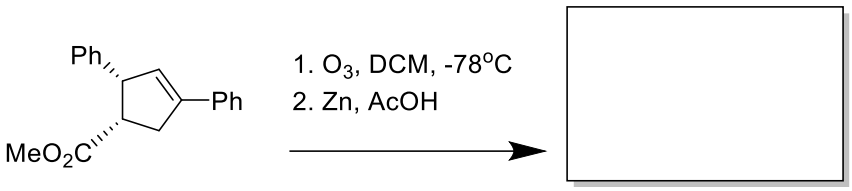
Mironov, V. F.; Nemtarev, A. V.; Tsepaeva, O. V.; Dimukhametov, M. N.; Litvinov, I. A.; Voloshina, A. D.; Pashirova, T. N.; Titov, E. A.; Lyubina, A. P.; Amerhanova, S. K.; Gubaidullin, A. T.; Islamov, D. R. Rational Design 2-Hydroxypropylphosphonium Salts as Cancer Cell Mitochondria-Targeted Vectors: Synthesis, Structure, and Biological Properties. *Molecules* 2021, *26* (21), 6350. https://doi.org/10.3390/molecules26216350

4b.1.26



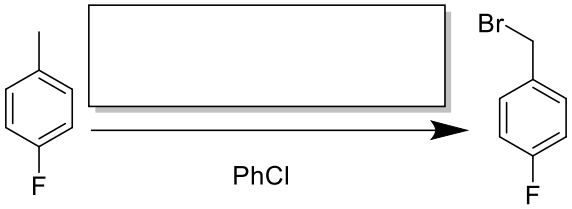
Mehta, G.; Singh, S. R.; Balanarayan, P.; Gadre, S. R. Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]Hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects. *Org. Lett.* 2002, *4* (14), 2297–2300. https://doi.org/10.1021/ol026005d

4b.1.27



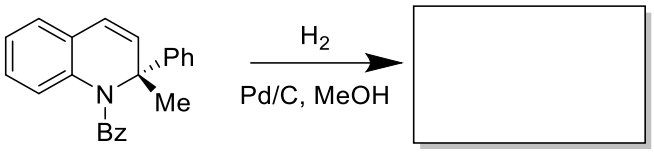
Zhao, J.; He, L.; Lv, H. Enantioselective Synthesis of Chiral Cyclopentenes by Relay Catalysis from Terminal Alkynes, Enones, and Syngas. *Org. Lett.* 2026, *28* (1), 202–207. https://doi.org/10.1021/acs.orglett.5c04598

4b.1.28



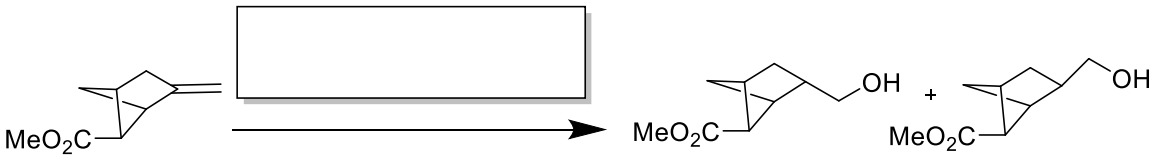
Steiner, A.; Williams, J. D.; De Frutos, O.; Rincón, J. A.; Mateos, C.; Kappe, C. O. Continuous Photochemical Benzylic Bromination Using *in Situ* Generated Br_2 : Process Intensification towards Optimal PMI and Throughput. *Green Chem.* 2020, *22* (2), 448–454. https://doi.org/10.1039/C9GC03662H

4b.1.29



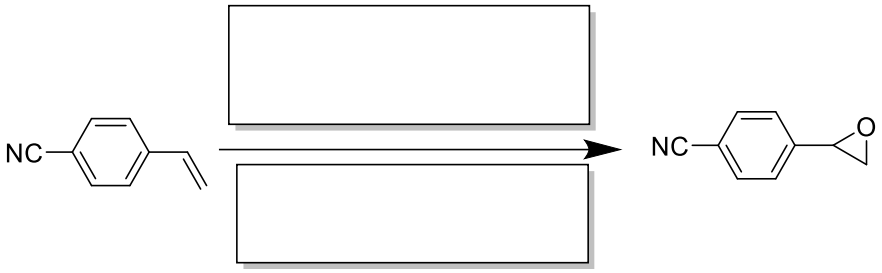
Huang, W.-J.; Chen, J.; Bai, Y.-Q.; Zhou, Y.-G.; Jiang, G.-F.; Wu, B. Asymmetric Synthesis of 2,2-Disubstituted Dihydroquinolines via Rhodium-Catalyzed Dearomative Arylation and Alkenylation of 2-Substituted Quinolinium Salts. *Org. Lett.* 2026, *28* (7), 2284–2288. https://doi.org/10.1021/acs.orglett.5c05303

4b.1.30



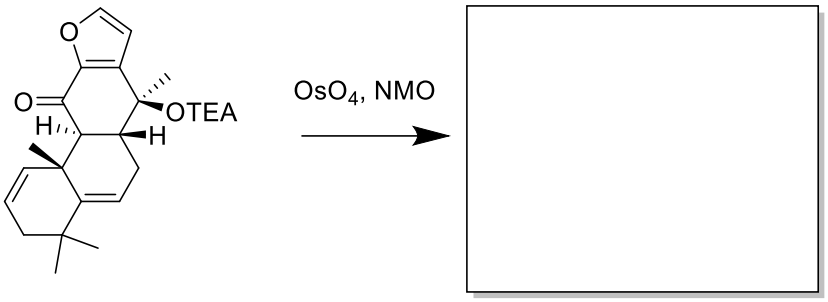
Mehta, G.; Singh, S. R.; Balanarayan, P.; Gadre, S. R. Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]Hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects. *Org. Lett.* 2002, *4* (14), 2297–2300. https://doi.org/10.1021/ol026005d

4b.1.31



Qin, L.; Li, M.; Wang, X.; You, C.; Deng, G.; Chen, Y. Engineering of $P450_{PL2}$ Monooxygenase for the Stereoselective Synthesis of (*R*)-Styrene Oxides. *Org. Lett.* 2026, *28* (8), 2567–2572. https://doi.org/10.1021/acs.orglett.5c05206

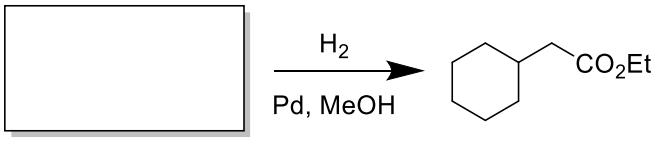
4b.1.32



Hint: The trisubstituted alkene is not accessible by the reagents.

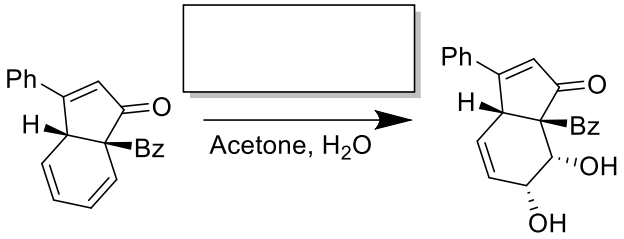
Papidocha, S. M.; Bulthaupt, H. H.; Carreira, E. M. Synthesis of Neocaesalpin A, AA, and Nominal Neocaesalpin K**. *Angew. Chem. Int. Ed.* 2023, *62* (48), e202310149. https://doi.org/10.1002/anie.202310149

4b.1.33



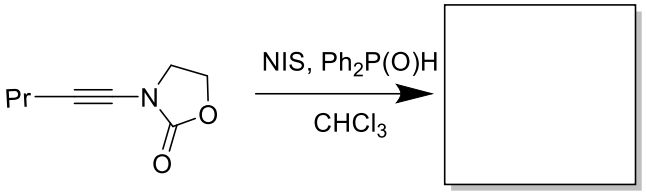
Golubev, V.; Phan, N. H. T.; Pohl, R.; Tarabek, J.; Císařová, I.; Jahn, U. A Synthetic Approach to Sterically Hindered P-Chiral Phosphine Ligands and Their Applications for Asymmetric Gold Catalysis. *Adv. Synth. Catal.* 2026, *368* (1), e70067. https://doi.org/10.1002/adsc.70067

4b.1.34



Lu, J.; Dong, H.; Wu, S.; Wang, C.; Lin, A.; Sun, P. Enantioselective Synthesis of Bicyclo[4.3.0]Nonatrienones via Palladium-Catalyzed Desymmetric 1,5-Enyne Cycloisomerization. *Org. Lett.* 2026, *28* (5), 1826–1831. https://doi.org/10.1021/acs.orglett.5c05377

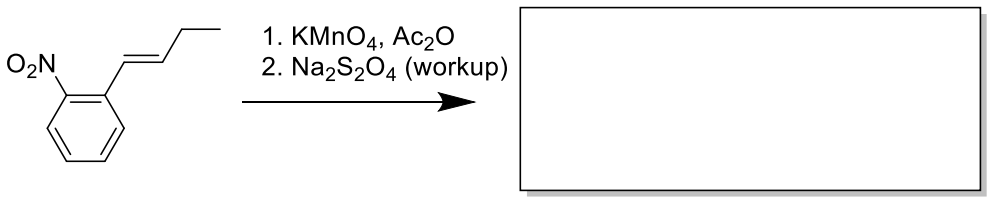
4b.1.35



Note: NIS is an iodine version of NBS. For introductory organic chemistry courses, you can ignore the use of $Ph_2P(O)H$.

Pati, S. S.; Mishra, A.; Das, J. P. Construction of Acyclic Vicinal All-Carbon Quaternary and Tertiary Carbon Stereocenters via a Stereoselective Claisen Rearrangement. *Org. Lett.* 2025, *27* (35), 9681-9686. https://doi.org/10.1021/acs.orglett.5c02876

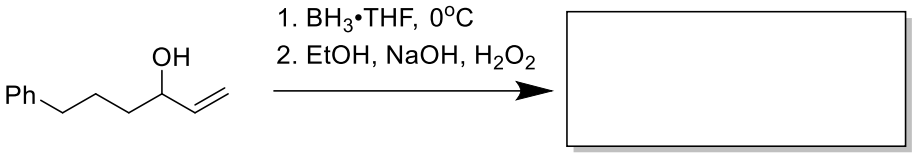
4b.1.36



Note: Sodium dithionite ($Na_2S_2O_4$) is a reducing agent that decomposes permanganate.

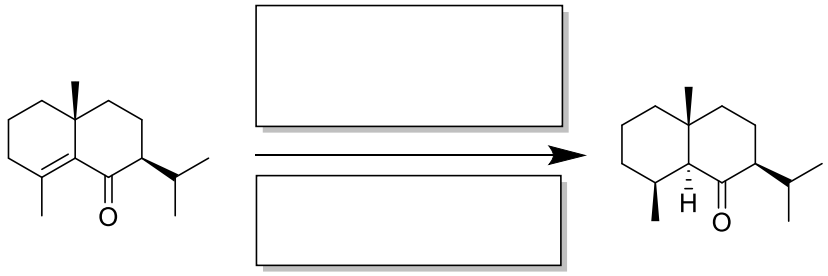
Racochote, S.; Nutthawasutha, C.; Bado, U.; Theppitak, C.; Tummatorn, J.; Ruchirawat, S.; Thongsornkleeb, C. Photoisomerization of Isatogens to Benzoxazin-4-Ones. *J. Org. Chem.* 2026, acs.joc.6c00639. https://doi.org/10.1021/acs.joc.6c00639

4b.1.37



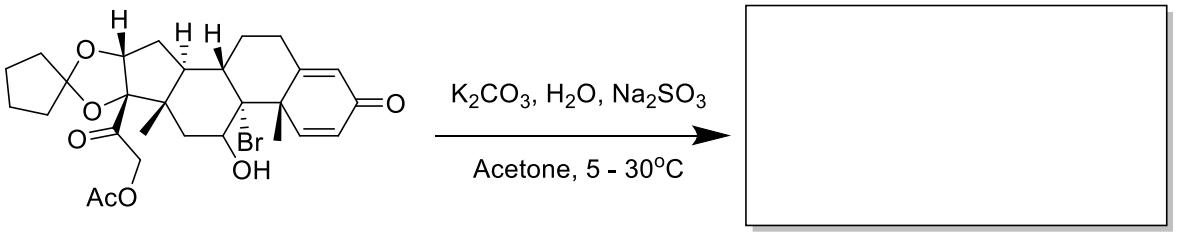
Liu, Z.; Breit, B. Rhodium-Catalyzed Regioselective Addition of *N* -Hydroxyl Imides to Internal Alkynes. *Isr. J. Chem.* 2026, *66* (3), e70014. https://doi.org/10.1002/ijch.70014

4b.1.38



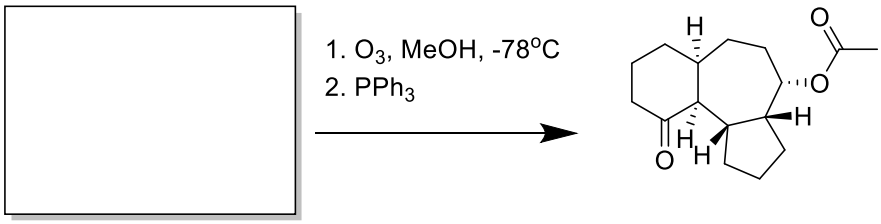
Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* 2009, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

4b.1.39



Kharpe, A. A.; Wagare, D. S.; Mokale, S.; Netankar, P. D. An Efficient Protocol for the Synthesis of Amcinonide from Tetraene Acetate. *Polycyclic Aromat. Compd.* 2025, *45* (7), 1367–1379. https://doi.org/10.1080/10406638.2025.2454256

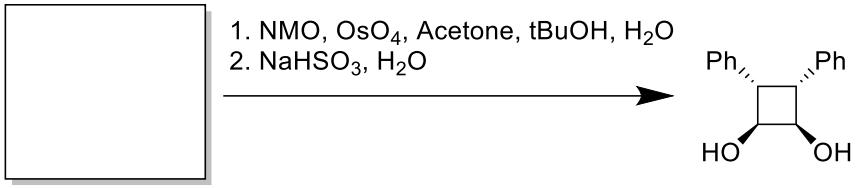
4b.1.40



Note: PPh_3 is a reducing agent analogous to DMS

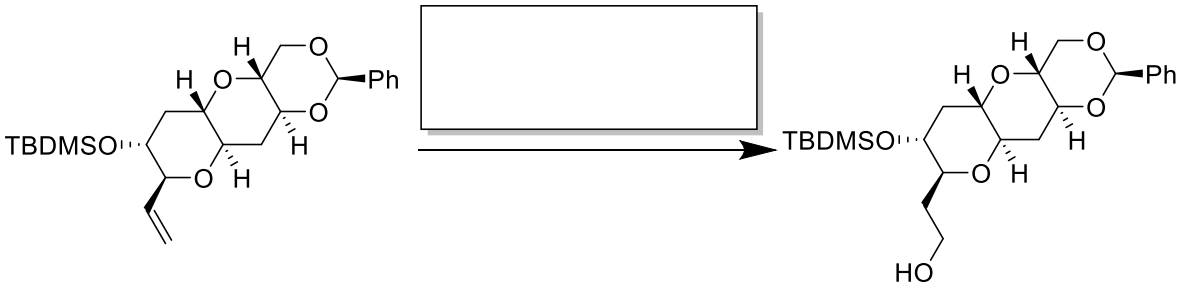
Wang, Z.; Zhang, Z.; Xie, X.; Qin, S.; Fu, S.; Liu, B. Construction of the Tricyclic Core of Rhamnofolane-Type Diterpenoids. *Org. Chem. Front.* 2026, *13* (5), 1617–1624. https://doi.org/10.1039/D5QO01699A

4b.1.41



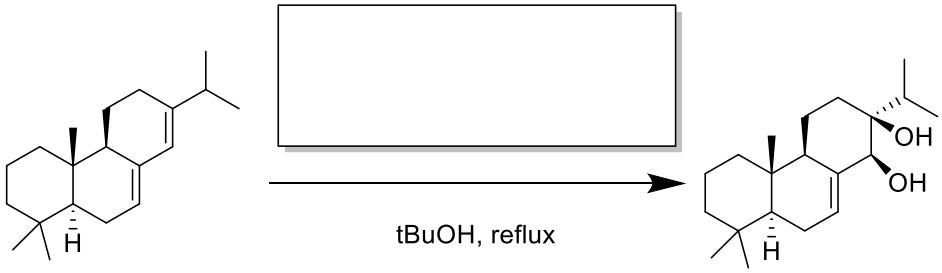
Zhao, R.; Zhou, D.-Y.; Asano, K.; Suzuki, T.; Suzuki, T. Stereodefined Synthesis of Acyclic *Meso* -2,3-Diaryl Dialdehydes and Their Iridium-Catalyzed Enantioselective Desymmetrization. *J. Org. Chem.* 2026, *91* (30), 10461–10465. https://doi.org/10.1021/acs.joc.6c00927

4b.1.42



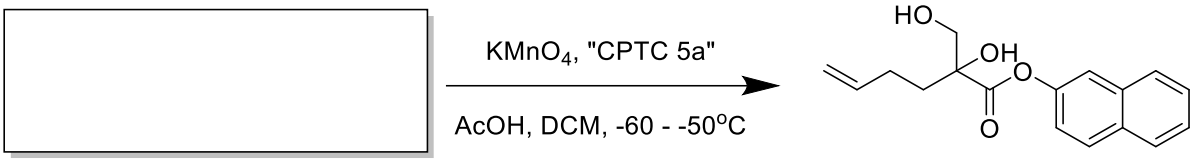
Moya-Utrera, F.; Cheng-Sánchez, I.; Fuentes-Pino, I.; Sánchez-Ruiz, A.; Sarabia, F. Efficient Synthesis of Fused Polycyclic Ether Systems via Sulfonium Ylides: A Synthetic Approach to Yessotoxin and Adriatoxin. *Marine Drugs* 2025, *23* (2), 51. https://doi.org/10.3390/md23020051

4b.1.43



Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. Enantioselective Total Synthesis of Cytotoxic Taiwaniaquinones A and F. *Chem. Commun.* 2010, *46* (48), 9244. https://doi.org/10.1039/c0cc03763j

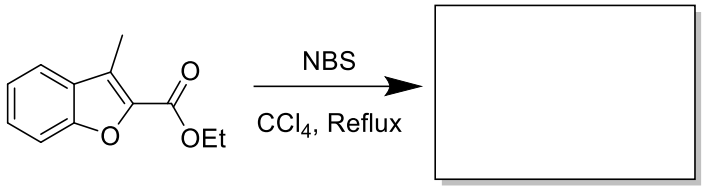
4b.1.44



Note: For introductory organic chemistry courses, you can ignore the catalyst CPTC 5a.

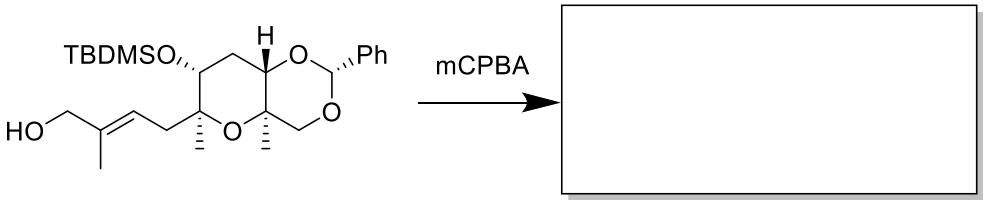
Rank, N. S.; Hussein, A. A.; Cecil, A. L.; Light, M. E.; Brown, R. C. D. Enantioselective Synthesis of Tetrahydrofurans by Permanganate-Mediated Oxidative Cyclisation of 1,5-Dienes Using Chiral Phase-Transfer Catalysis. *Org. Chem. Front.* 2026, *13* (13), 4078–4088. https://doi.org/10.1039/D6QO00377J

4b.1.45



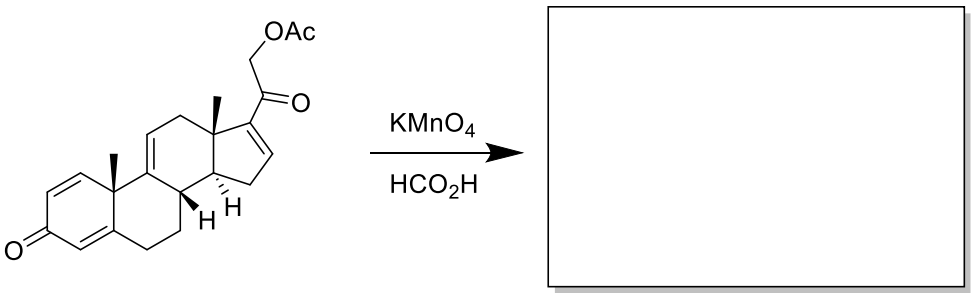
Eldehna, W. M.; Tawfik, H. O.; Nafie, M. S.; Al Kamaly, O.; El-Hamaky, A. A.; El Hassab, M. A.; Elsayed, Z. M.; Elnaggar, Y. S. R.; Al-Karmalawy, A. A.; Di Giacomo, V.; Balaha, M. Novel Benzofuran-Conjugated Indolin-2-Ones as Anticancer Agents: Design, Synthesis, Biological Assessments, and Molecular Modeling Insights. *Bioorg. Chem.* 2025, *160*, 108494. https://doi.org/10.1016/j.bioorg.2025.108494

4b.1.46



Moya-Utrera, F.; Cheng-Sánchez, I.; Fuentes-Pino, I.; Sánchez-Ruiz, A.; Sarabia, F. Efficient Synthesis of Fused Polycyclic Ether Systems via Sulfonium Ylides: A Synthetic Approach to Yessotoxin and Adriatoxin. *Marine Drugs* 2025, *23* (2), 51. https://doi.org/10.3390/md23020051

4b.1.47



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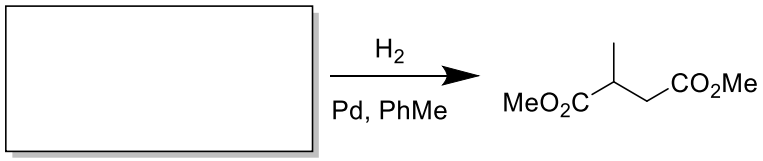
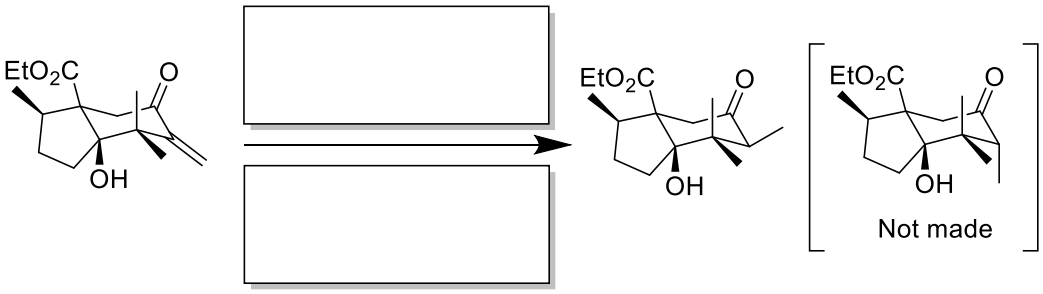


Golubev, V.; Phan, N. H. T.; Pohl, R.; Tarabek, J.; Císařová, I.; Jahn, U. A Synthetic Approach to Sterically Hindered P-Chiral Phosphine Ligands and Their Applications for Asymmetric Gold Catalysis. *Adv. Synth. Catal.* 2026, *368* (1), e70067. https://doi.org/10.1002/adsc.70067

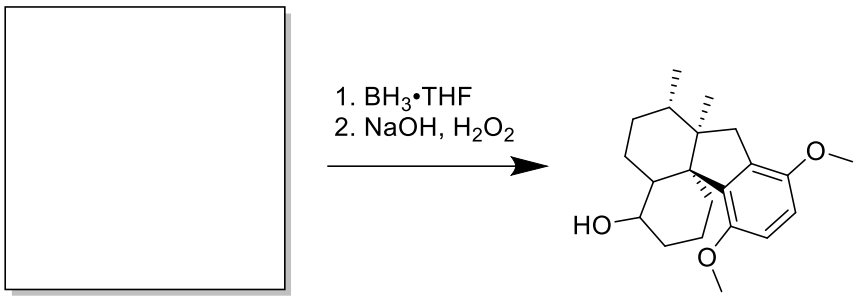
4b.1.49



Note: Explain why after hydrogenation and then base, only the specific stereoisomer is made.

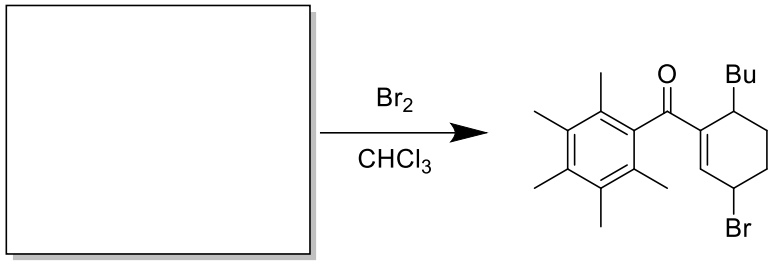
Fu, P.; Liu, T.; Shen, Y.; Lei, X.; Xiao, T.; Chen, P.; Qiu, D.; Wang, Z.; Zhang, Y. Divergent Total Syntheses of *Illicium* Sesquiterpenes through Late-Stage Skeletal Reorganization. *J. Am. Chem. Soc.* 2023, *145* (33), 18642–18648. https://doi.org/10.1021/jacs.3c06442

4b.1.50



Chong, C.; Chang, L.; Grimm, I.; Zhang, Q.; Kuang, Y.; Wang, B.; Kang, J.; Liu, W.; Baars, J.; Guo, Y.; Schmalz, H.-G.; Lu, Z. Divergent Total Synthesis of the Revised Structures of Marine Anti-Cancer Meroterpenoids (+)-Dysiherbols A-E. *Chem. Sci.* 2023. *14* (12). 3302-3310. https://doi.org/10.1039/d3sc00173c

4b.1.51

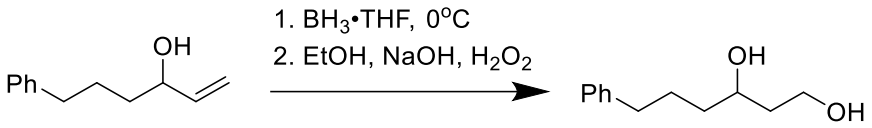


Amer, M. M.; Hou, J.; Wang, J.; Mazeikaite, A.; Donohoe, T. J. Asymmetric Hydride Shift Reactions Catalyzed by Chiral Aluminium Complexes. *Angew. Chem. Int. Ed.* 2026, *65* (5), e202521374. https://doi.org/10.1002/anie.202521374

Section 4b – Mechanism Questions

Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

4b.2.1



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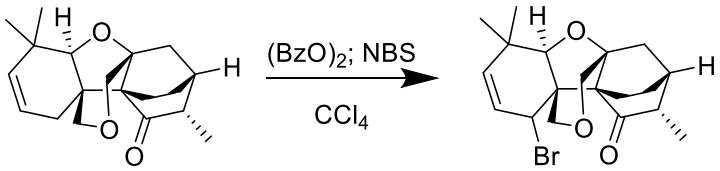
4b.2.2



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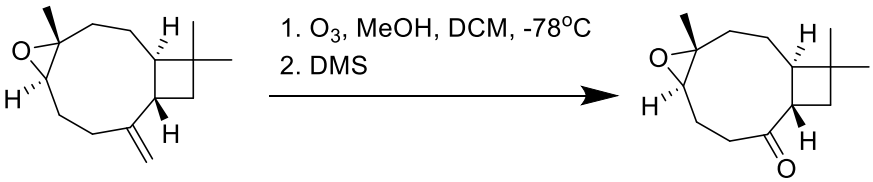
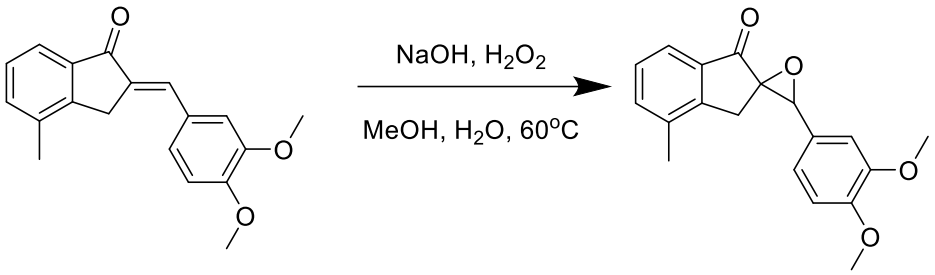
4b.2.3



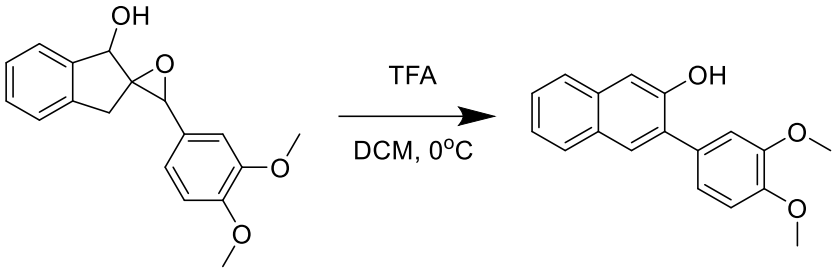
Prout, E. S.; Kwon, O.; Silva, T. G. Regioselective Synthesis of Methyl Enol Ethers from Cycloalkanones via O-Methylation of Kinetic Enolates. *Synthesis* 2026, *58* (13), 1527–1538. https://doi.org/10.1055/a-2822-8676

4b.2.4



Story, J. B.; Ringler, K. E.; Nguyen, C. L.; Drance, M. J.; Howard, E. M. Synthesis of 2-Naphthols via a Trifluoroacetic Acid-Mediated Epoxy Alcohol Rearrangement. *J. Org. Chem.* 2026, *91* (14), 5249–5254. https://doi.org/10.1021/acs.joc.6c00021

4b.2.5



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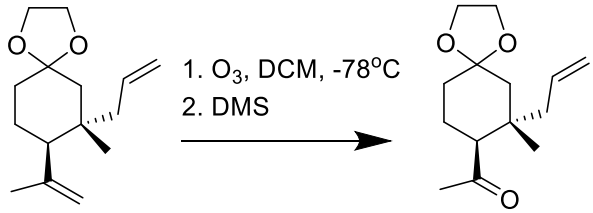
4b.2.6



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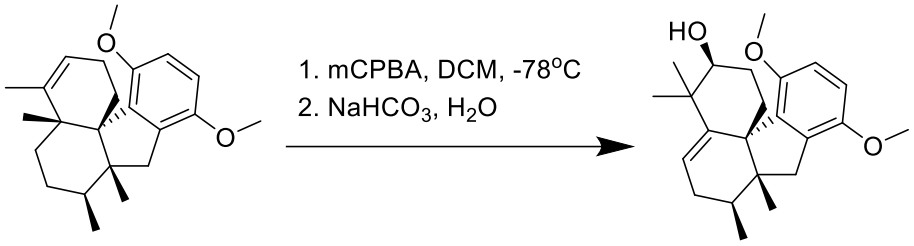

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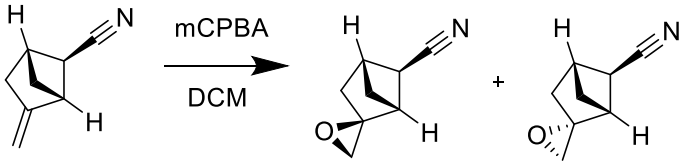

36 : 64

Mehta, G.; Singh, S. R.; Balanarayan, P.; Gadre, S. R. Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]Hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects. *Org. Lett.* 2002, *4* (14), 2297–2300. https://doi.org/10.1021/ol026005d

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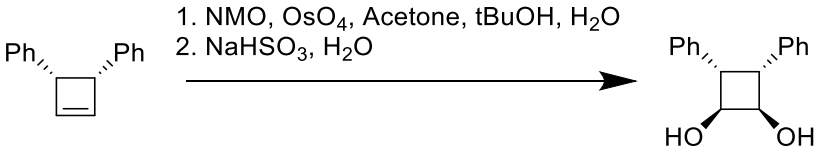

Zhao, R.; Zhou, D.-Y.; Asano, K.; Suzuki, T.; Suzuki, T. Stereodefined Synthesis of Acyclic *Meso* -2,3-Diaryl Dialdehydes and Their Iridium-Catalyzed Enantioselective Desymmetrization. *J. Org. Chem.* 2026, *91* (30), 10461–10465. https://doi.org/10.1021/acs.joc.6c00927

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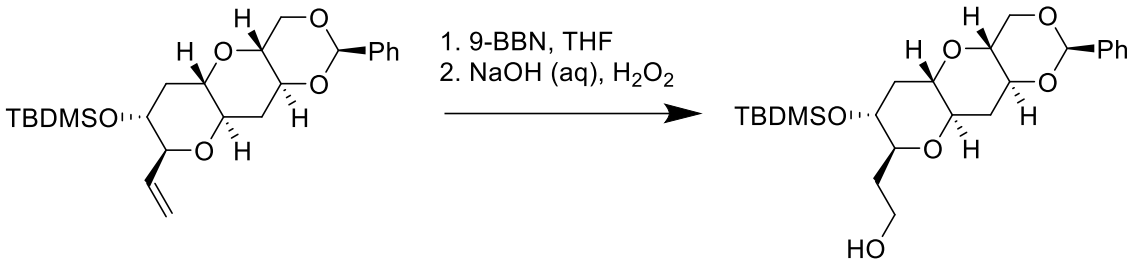

Moya-Utrera, F.; Cheng-Sánchez, I.; Fuentes-Pino, I.; Sánchez-Ruiz, A.; Sarabia, F. Efficient Synthesis of Fused Polycyclic Ether Systems via Sulfonium Ylides: A Synthetic Approach to Yessotoxin and Adriatoxin. *Marine Drugs* 2025, *23* (2), 51. https://doi.org/10.3390/md23020051

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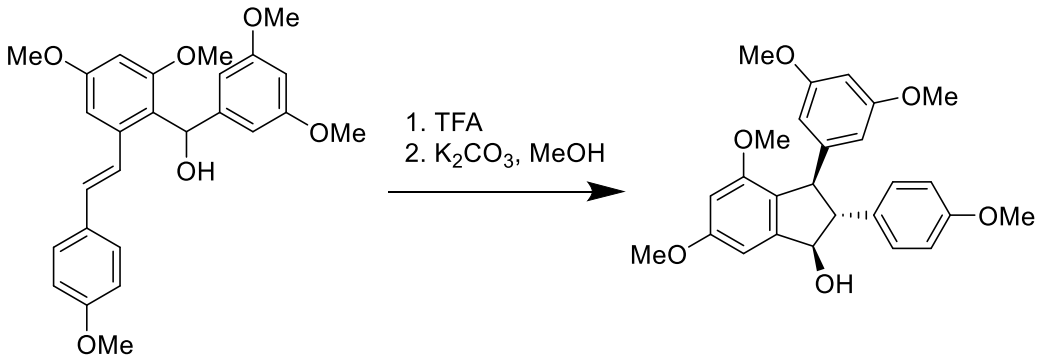

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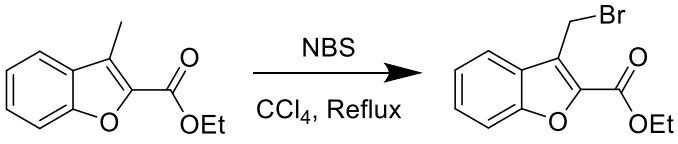

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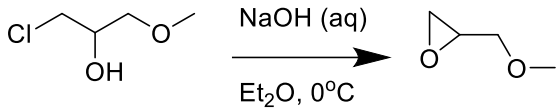
4b.2.13



Mironov, V. F.; Nemtarev, A. V.; Tsepaeva, O. V.; Dimukhametov, M. N.; Litvinov, I. A.; Voloshina, A. D.; Pashirova, T. N.; Titov, E. A.; Lyubina, A. P.; Amerhanova, S. K.; Gubaidullin, A. T.; Islamov, D. R. Rational Design 2-Hydroxypropylphosphonium Salts as Cancer Cell Mitochondria-Targeted Vectors: Synthesis, Structure, and Biological Properties. *Molecules* 2021, *26* (21), 6350. https://doi.org/10.3390/molecules26216350

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Mehta, G.; Singh, S. R.; Balanarayan, P.; Gadre, S. R. Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]Hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects. *Org. Lett.* 2002, *4* (14), 2297–2300. https://doi.org/10.1021/ol026005d

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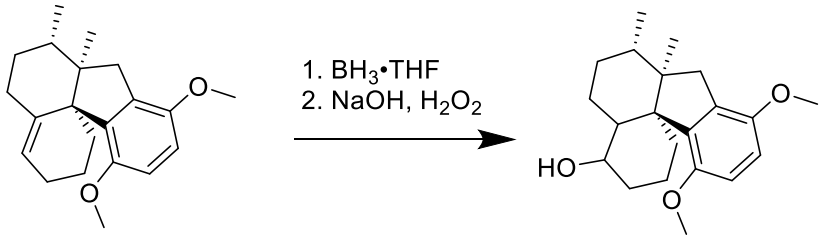

Chong, C.; Chang, L.; Grimm, I.; Zhang, Q.; Kuang, Y.; Wang, B.; Kang, J.; Liu, W.; Baars, J.; Guo, Y.; Schmalz, H.-G.; Lu, Z. Divergent Total Synthesis of the Revised Structures of Marine Anti-Cancer Meroterpenoids (+)-Dysiherbols A-E. *Chem. Sci.* 2023. *14* (12). 3302-3310. https://doi.org/10.1039/d3sc00173c

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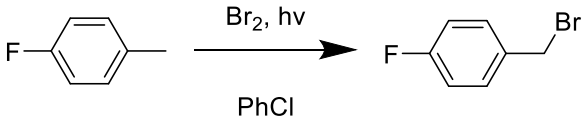

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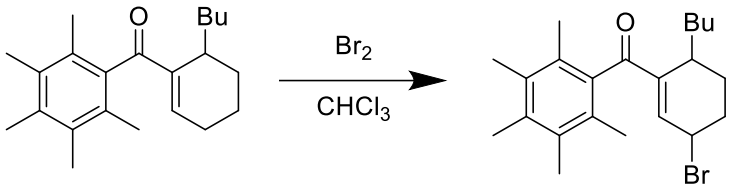


Amer, M. M.; Hou, J.; Wang, J.; Mazeikaite, A.; Donohoe, T. J. Asymmetric Hydride Shift Reactions Catalyzed by Chiral Aluminium Complexes. *Angew. Chem. Int. Ed.* 2026, *65* (5), e202521374. https://doi.org/10.1002/anie.202521374

Section 5: Alkynes

Required foundation for this section:

Formation of alkynes

Deprotonation of terminal alkynes and its alkylation

Electrophilic addition of HX / X_2

Acid-catalyzed hydration with $HgSO_4$ (tautomerization)

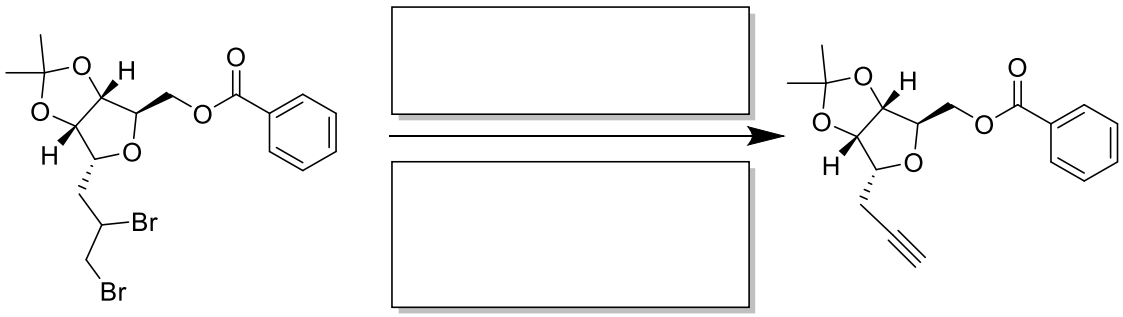
Hydroboration-oxidation

Partial and full reduction

Section 5 – Box-Type Questions

For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

5.1.1



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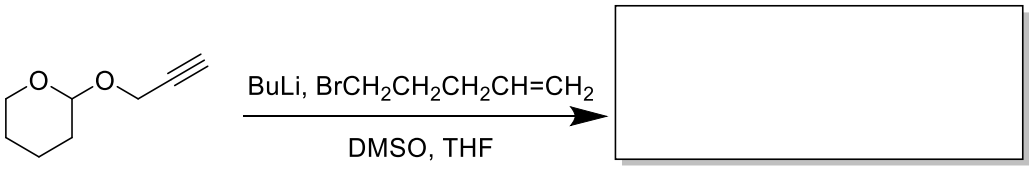
5.1.2



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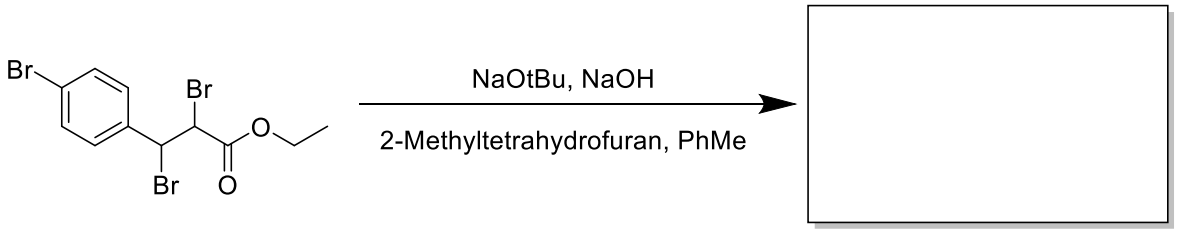
5.1.3



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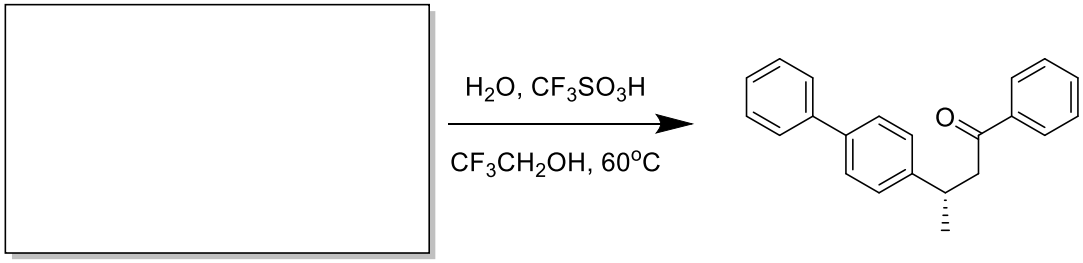
5.1.4



Gao, Z.; Xu, D.-D.; Fan, L.-W.; Luo, Q.; Zhou, Z.-J.; Dong, X.-Y.; Li, Z.-L.; Liu, X.-Y. Copper-Catalyzed Enantioconvergent Radical Deborylative Coupling of Racemic Benzylboronic Esters with Alkynes and Alkenylboronic Esters. *J. Am. Chem. Soc.* 2026, *148* (7), 7655–7662. https://doi.org/10.1021/jacs.5c21668

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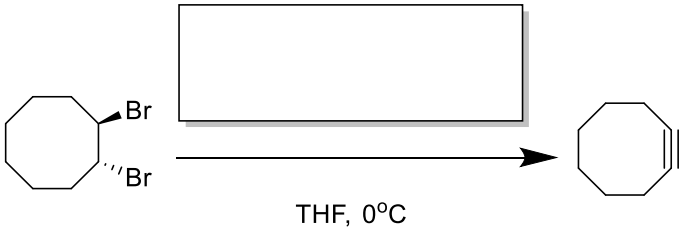

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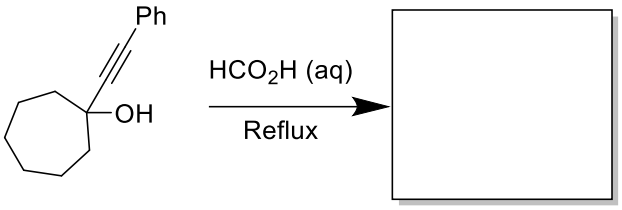

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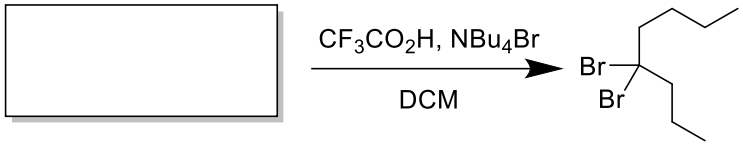
5.1.7



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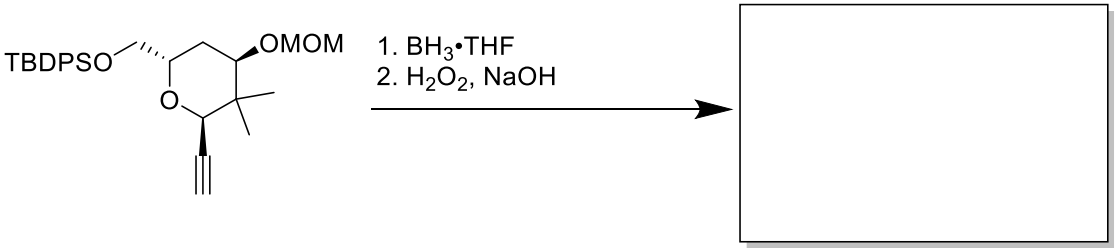

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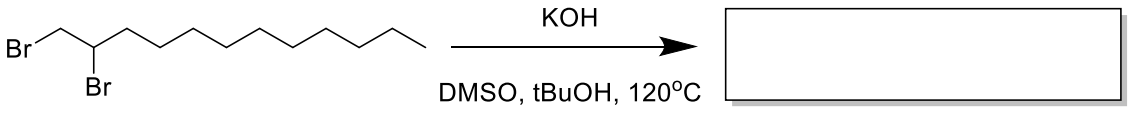
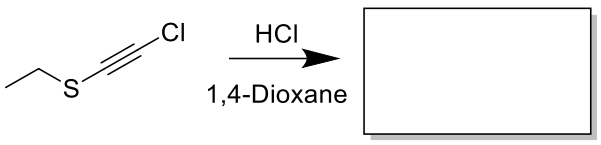
5.1.9



Kumaki, W.; Kinoshita, H.; Miura, K. Regio- and Stereoselective Synthesis of Bromoalkenes by Homolytic Hydrobromination of Alkynes with Hydrogen Bromide. *Tetrahedron* 2022, *110*, 132687. https://doi.org/10.1016/j.tet.2022.132687

5.1.10



D'yachkova, S. G.; Nikitina, E. A.; Gusarova, N. K. (Organylthio)chloroacetylenes: VII. Hydrochlorination of (Alkylthio)chloroacetylenes. *Russ. J. Gen. Chem.* 2003, *73* (8), 1246-1248. https://doi.org/10.1023/B:RUGC.0000007649.71394.73

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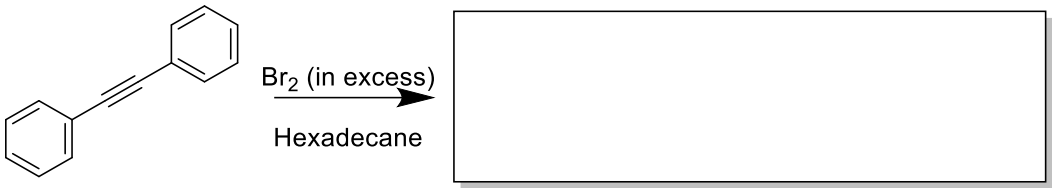
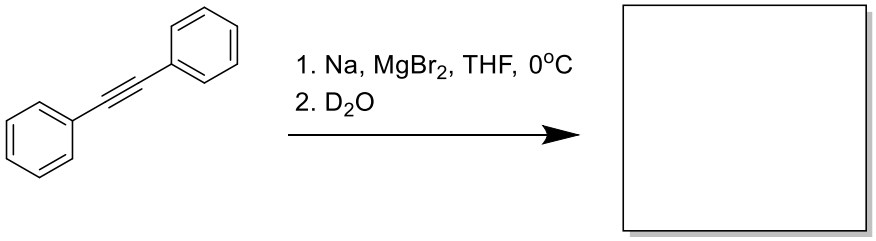


The authors isolated two products, with one in higher quantity than the other.

Ma, K.; Li, S.; Weiss, R. G. Stereoselective Bromination Reactions Using Tridecylmethylphosphonium Tribromide in a "Stacked" Reactor. *Org. Lett.* 2008, *10* (19), 4155–4158.

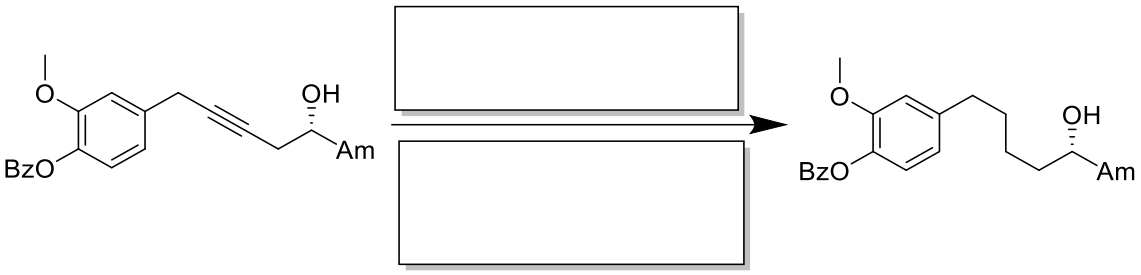
5.1.12



Note: The $MgBr_2$ displaces the Na after the reduction step to stabilize the carbanion.

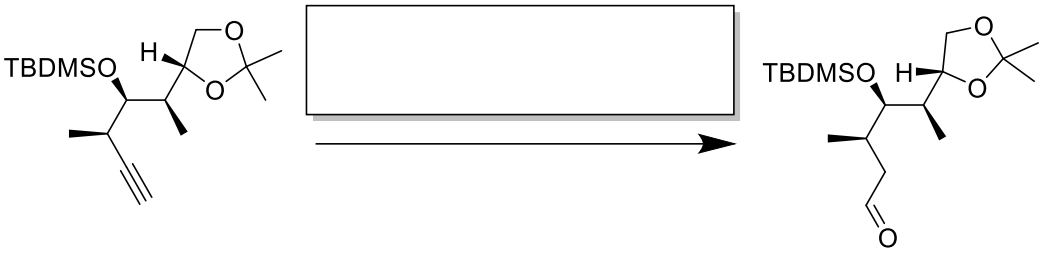
Yamaguchi, H.; Takahashi, F.; Kurogi, T.; Yorimitsu, H. Sodium-Mediated Reductive *anti*-Dimagnesiation of Diarylacetylenes with Magnesium Bromide. *Synthesis* 2024, *56* (21), 3307-3313. https://doi.org/10.1055/a-2326-6416

5.1.13



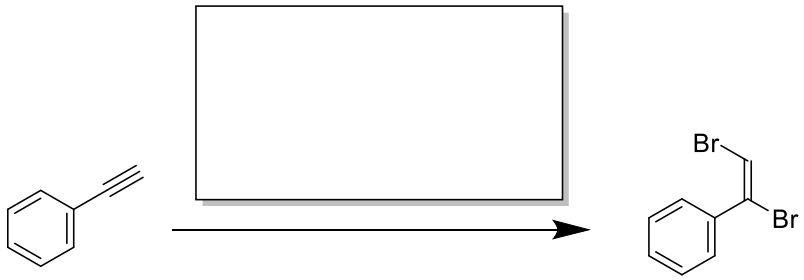
Shet, M. N.; Ramana, C. V. Total Synthesis of (−) and (+)-Zingibergingerols A. *J. Org. Chem.* 2024, *89* (22), 16923–16928. https://doi.org/10.1021/acs.joc.4c01649

5.1.14



Vintonyak, V. V.; Maier, M. E. Synthesis of the Core Structure of Cruentaren A. *Org. Lett.* 2007, *9* (4), 655–658. https://doi.org/10.1021/ol0629317

5.1.15



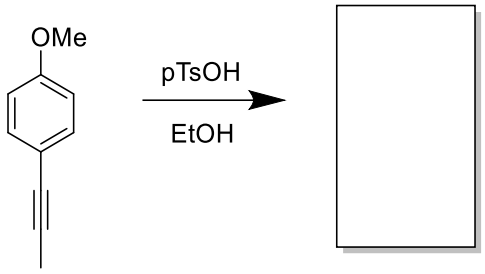
CCl_4

Dominant product

Note: H_2O_2 is an oxidant to convert the bromide to molecular bromine (Br_2).

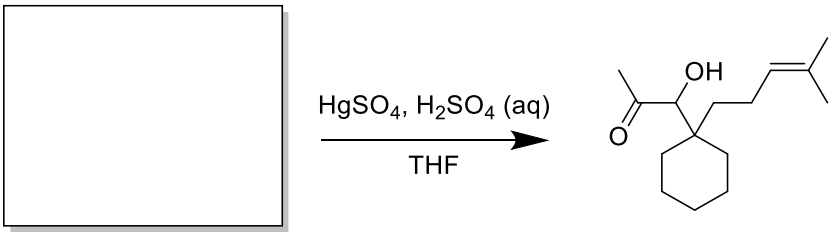
Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. Simple and Practical Halogenation of Arenes, Alkenes and Alkynes with Hydrohalic Acid/H202 (or TBHP). *Tetrahedron* 1999, *55* (36), 11127-11142. https://doi.org/10.1016/s0040-4020(99)00628-6

5.1.16



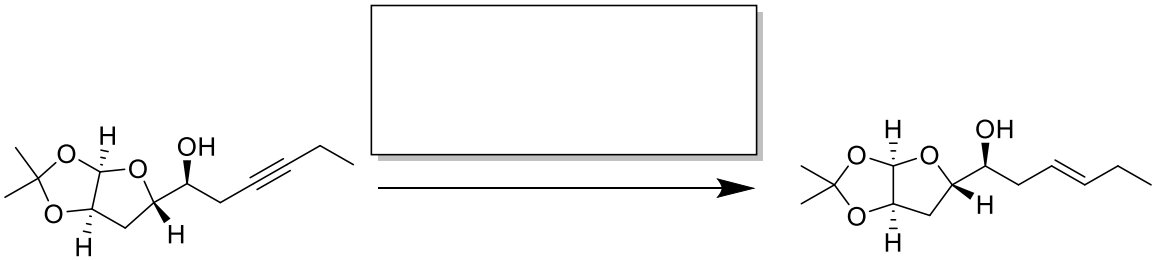
Alkahtani, R.; Westphäling, J.; Gorecka, A.; Babaahmadi, R.; Gieman, H.; Finance, M.; Lorente-Martinez, J.; Bhattacherjee, D.; Melen, R. L.; Baik, M.-H.; Wirth, T. Oxidative Rearrangement of Alkynes to Chiral α-Arylalkanoic Esters. *Chem. Sci.* 2026, *17* (2), 1318–1324. https://doi.org/10.1039/D5SC07882B

5.1.17



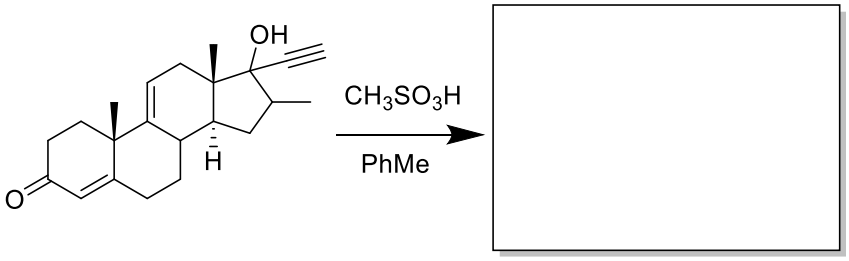
Vulovic, B.; Trmcic, M.; Matovic, R.; Saicic, R. N. Cyclization Reactions of Oxyallyl Cation. A Method for Cyclopentane Ring Formation. *Org. Lett.* 2019, *21* (23), 9618–9621. https://doi.org/10.1021/acs.orglett.9b03791

5.1.18



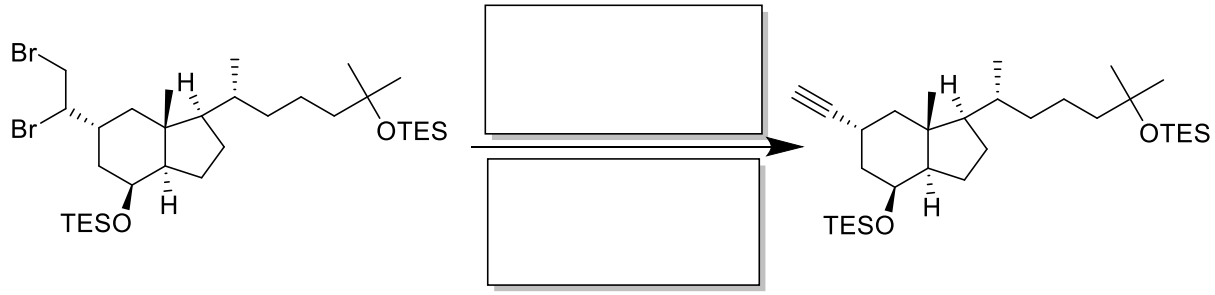
Senapati, S.; Unmesh, N. A.; Shet, M. N.; Ahmad, I.; Ajikumar, N.; Ramana, C. V. Unified Approach for the Total Synthesis of Bis-THF C15 Acetogenins: A Chloroenyne from *Laurencia majuscula*, Laurendecumenyne B and Laurefurenynes A/B. *Synthesis* 2021, *53* (16), 2903-2910. https://doi.org/10.1055/a-1500-1407

5.1.19



Wei, J.; Zhang, Y.; Liu, M.; Ning, Y.; Cao, Y.; Chen, F. Divergent Chemo- and Biocatalytic Route to 16 *β* -Methylcorticoids: Asymmetric Synthesis of Betamethasone Dipropionate, Clobetasol Propionate, and Beclomethasone Dipropionate. *Angew. Chem. Int. Ed.* 2024, *63* (4), e202313952. https://doi.org/10.1002/anie.202313952

5.1.20



Iwaki, M.; Sakamoto, R.; Tsutsumi, R.; Sawada, T.; Hirokawa, T.; Kato, S.; Nagasawa, K. Development of an Environmentally Responsive Fluorescent Ligand for Vitamin D Receptor. *ChemBioChem* 2025, *26* (8), e202401038. https://doi.org/10.1002/cbic.202401038

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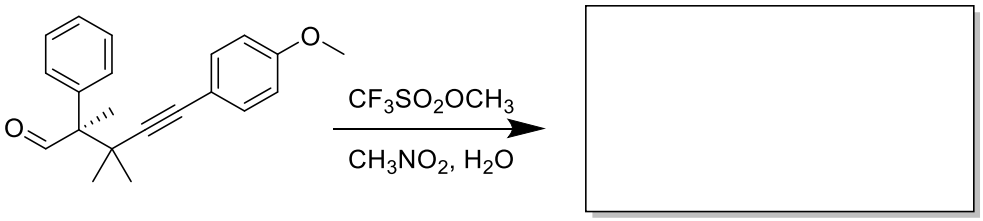
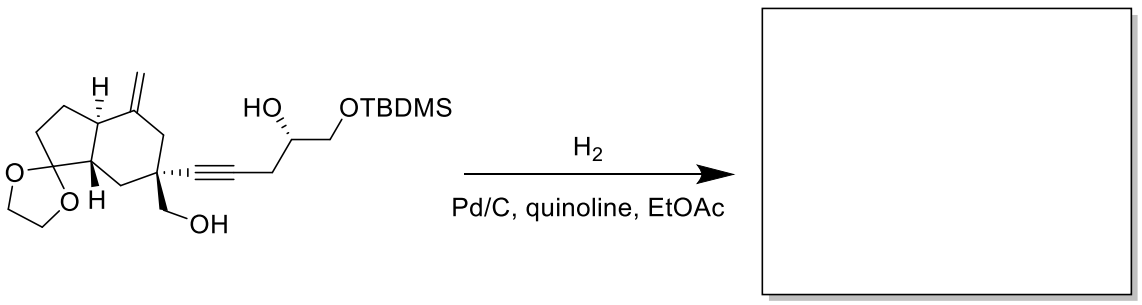


Note: Methyltriflate ($CF_3SO_2OCH_3$) reacts with water to form triflic acid (CF_3SO_2OH) and methanol.

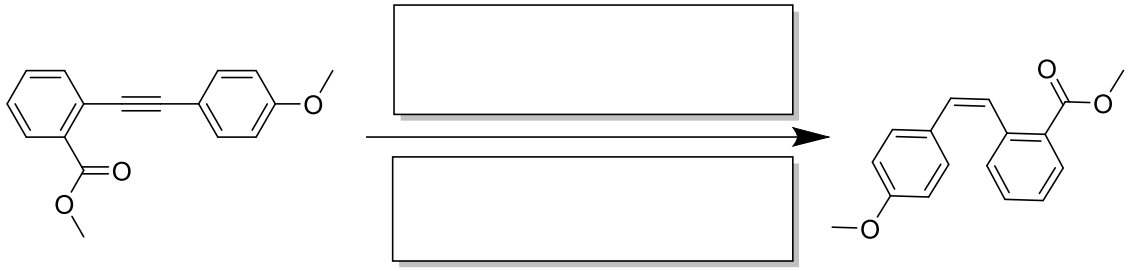
Wu, S.; Xu, X.; Tang, T.; Deng, X.; Zhang, S.; Yan, C.-G.; Zhang, J.; Wang, M.; Wang, L. Enantioselective Synthesis of Quaternary Stereocenter Aldehydes by Palladium-Catalyzed Intermolecular Propargylation Reaction. *J. Am. Chem. Soc.* 2026, *148* (15), 16058–16067. https://doi.org/10.1021/jacs.6c00417

5.1.22



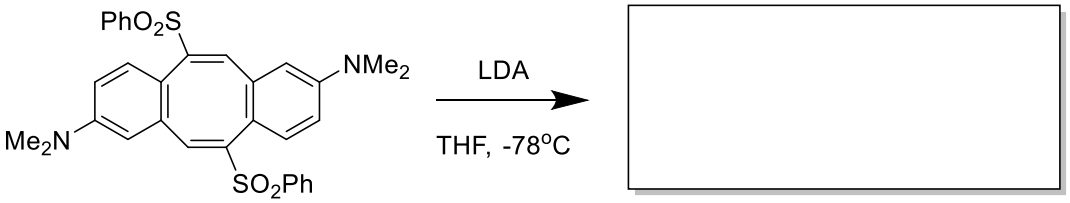
Zhang, Y.; Milkovits, A.; Agarawal, V.; Taylor, C. A.; Snyder, S. A. Total Synthesis of the Meroterpenoid Manginoid A as Fueled by a Challenging Pinacol Coupling and Bicycle-forming Etherification. *Angew. Chem. Int. Ed.* 2021, *60* (20), 11127–11132. https://doi.org/10.1002/anie.202016178

5.1.23



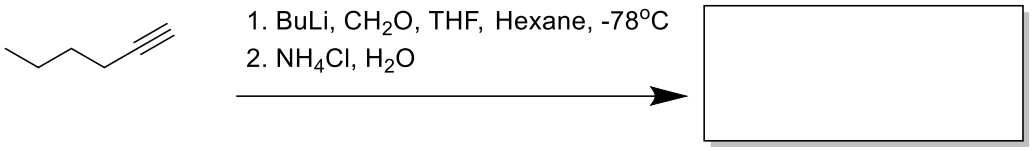
Sugano, M.; Fujiwara, T.; Mochizuki, W.; Inokuma, T.; Yamada, K. Catalyst-Controlled Regioselectivity Switching Inthe Bromolactonization of (*Z*)-StilbenecarboxylicAcids. *Org. Lett.* 2026, *28* (28), 8872–8877. https://doi.org/10.1021/acs.orglett.6c02195

5.1.24



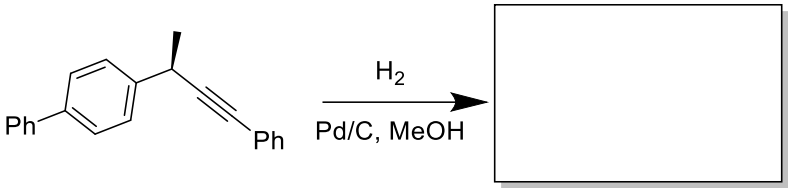
Sharma, K.; Strizhak, A. V.; Fowler, E.; Wang, X.; Xu, W.; Hatt Jensen, C.; Wu, Y.; Sore, H. F.; Lau, Y. H.; Hyvönen, M.; Itzhaki, L. S.; Spring, D. R. Water-Soluble, Stable and Azide-Reactive Strained Dialkynes for Biocompatible Double Strain-Promoted Click Chemistry. *Org. Biomol. Chem.* 2019, *17* (34), 8014-8018. https://10.1039/c9ob01745c

5.1.25



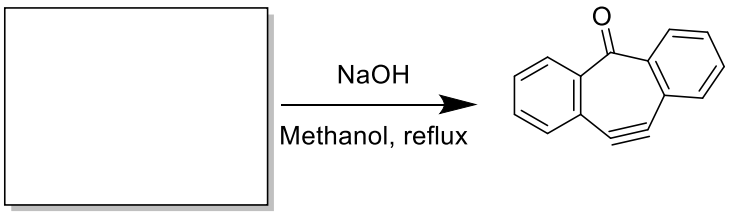
Ramesh, G.; Mishra, S.; Baire, B. A Hydrido-Alkynyl-Prins Cyclization Using Isopropanol as a Hydride Donor: Discovery, Scope and Mechanistic Study. *Org. Biomol. Chem.* 2026, *24* (25), 5355–5362. https://doi.org/10.1039/D6OB00688D

5.1.26



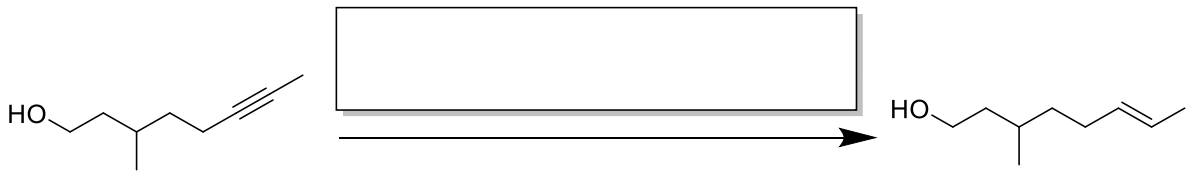
Gao, D.; Qin, L.-Z.; Li, Z.-L.; Gu, Q.-S.; Liu, X.-Y. Copper-Catalysed Enantioconvergent Radical C(Sp3)–C(Sp3) Cross-Coupling of Tertiary Electrophiles with Cyclopropanols for Quaternary Carbon Formation. *Nat. Synth.* 2026, *5* (5), 750–760. https://doi.org/10.1038/s44160-025-00987-1

5.1.27



Kornmayer, S.; Rominger, F.; Gleiter, R. Synthesis of 11,12-Didehydrodibenzo[a,e]Cycloocten-5(6H)-One: A Strained Eight-Membered Alkyne. *Synthesis* 2009, *2009* (15), 2547–2552. https://doi.org/10.1055/s-0029-1217404

5.1.28

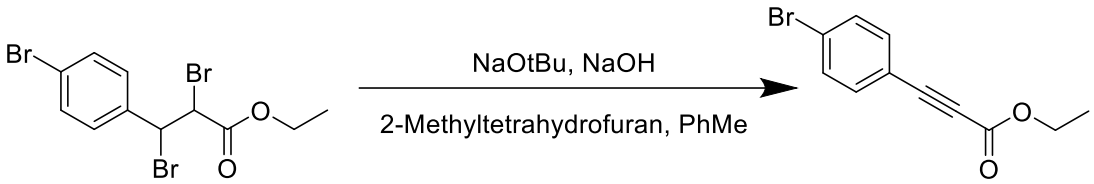


Vulovic, B.; Trmcic, M.; Matovic, R.; Saicic, R. N. Cyclization Reactions of Oxyallyl Cation. A Method for Cyclopentane Ring Formation. *Org. Lett.* 2019, *21* (23), 9618–9621. https://doi.org/10.1021/acs.orglett.9b03791

Section 5 – Mechanism Questions

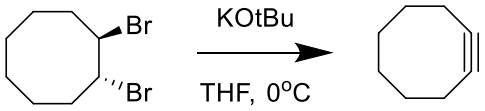
Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

5.2.1



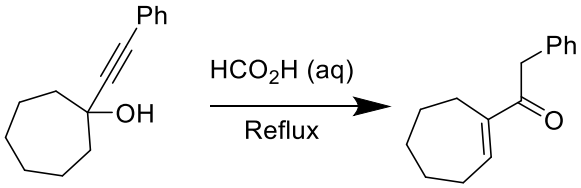
Chen, J.; Chen, T.; Hu, Q.; Püntener, K.; Ren, Y.; She, J.; Du, Z.; Scalone, M. Practical Asymmetric Hydrogenation-Based Synthesis of a Class-Selective Histone Deacetylase Inhibitor. *Org. Process Res. Dev.* 2014, *18* (12), 1702–1713. https://doi.org/10.1021/op500250b

5.2.2



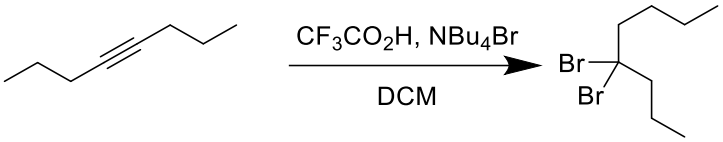
Lu, C.; Zhang, M.; Bai, T.; Yan, Z.; Pu, X.; Huang, X.; Chang, J.; Wang, Z.; Bai, X. Iron-Catalysed 1,4-Reduction of Quinones for the Synthesis of Hydroquinones. *Org. Biomol. Chem.* 2026, *24* (7), 1522–1527. https://doi.org/10.1039/D5OB01911G

5.2.3



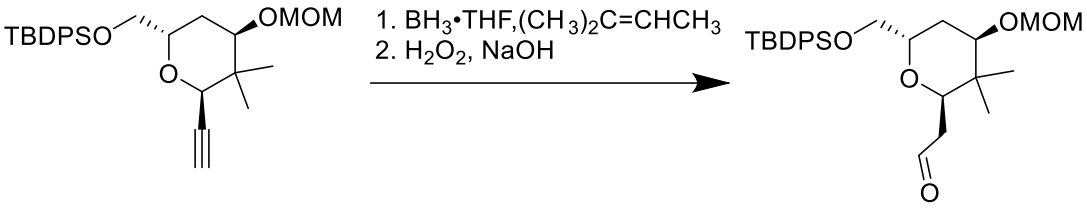
Scarpi, D.; Visi, S.; Muzzu, A.; Occhiato, E. G. One-Pot Gold(I)-Catalyzed Rautenstrauch Rearrangement/Nitrosocarbonyl Hetero-Diels–Alder Reaction Sequence for the Synthesis of α-Hydroxylated Cyclopentenones. *Eur. J. Org. Chem.* 2026. *29* (27), e70611. https://doi.org/10.1002/ejoc.70611

5.2.4



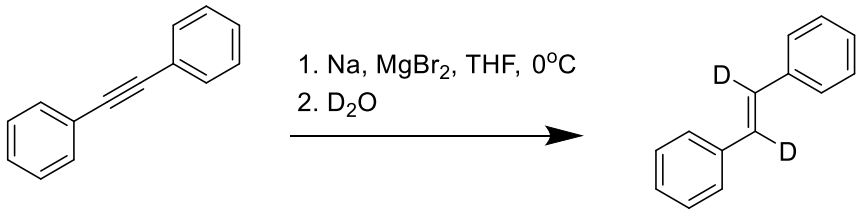
Weiss, H. M.; Touchette, K. M. Bromide Assisted Addition of Hydrogen Bromide to Alkynes and Allenes. *J. Chem. Soc., Perkin Trans. 2.* 1998, No. 6, 1523–1528. https://doi.org/10.1039/a703569a

5.2.5



Shangguan, N.; Kiren, S.; Williams, L. J. A Formal Synthesis of Psymberin. *Org. Lett.* 2007, *9* (6), 1093–1096. https://doi.org/10.1021/ol063143k

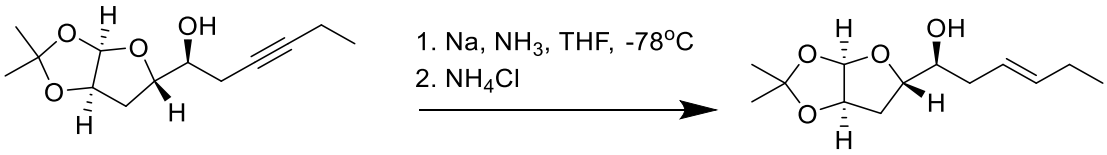
5.2.6



Note: the $MgBr_2$ displaces the Na after the reduction step to stabilize the carbanion.

Yamaguchi, H.; Takahashi, F.; Kurogi, T.; Yorimitsu, H. Sodium-Mediated Reductive *anti*-Dimagnesiation of Diarylacetylenes with Magnesium Bromide. *Synthesis* 2024, *56* (21), 3307-3313. https://doi.org/10.1055/a-2326-6416

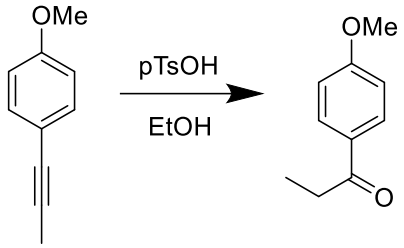
5.2.7



Senapati, S.; Unmesh, N. A.; Shet, M. N.; Ahmad, I.; Ajikumar, N.; Ramana, C. V. Unified Approach for the Total Synthesis of Bis-THF C15 Acetogenins: A Chloroenyne from *Laurencia majuscula*,

Laurendecumenyne B and Laurefurenynes A/B. *Synthesis* 2021, *53* (16), 2903-2910. https://doi.org/10.1055/a-1500-1407

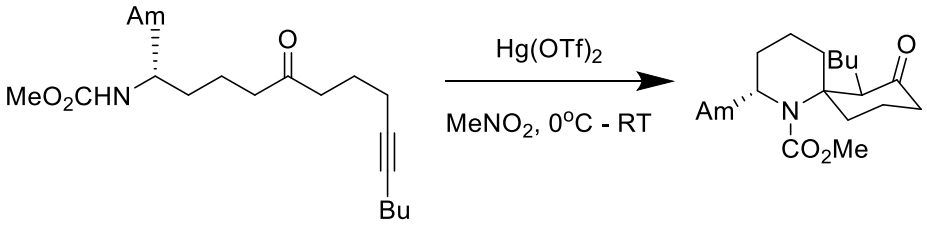
5.2.8



Note: Assume there's no water present so you will need to use only the reagents indicated.

Alkahtani, R.; Westphäling, J.; Gorecka, A.; Babaahmadi, R.; Gieman, H.; Finance, M.; Lorente-Martinez, J.; Bhattacherjee, D.; Melen, R. L.; Baik, M.-H.; Wirth, T. Oxidative Rearrangement of Alkynes to Chiral α-Arylalkanoic Esters. *Chem. Sci.* 2026, *17* (2), 1318–1324. https://doi.org/10.1039/D5SC07882B

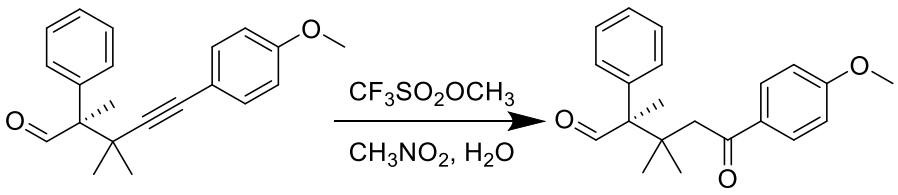
5.2.9



Hint: Nucleophilic addition, oxymercuration, and iminium reduction.

Nishikawa, K.; Ono, Y.; Mori, S.; Takayama, K.; Ihara, M.; Matsuda, K.; Morimoto, Y. Divergent Nine-Step Syntheses of Perhydrohistrionicotoxin Analogs and Their Inhibition Activity Toward Chicken A4β2-Neuronal Nicotinic Acetylcholine Receptors. *J. Org. Chem.* 2024, *89* (6), 4128–4133. https://doi.org/10.1021/acs.joc.3c02988

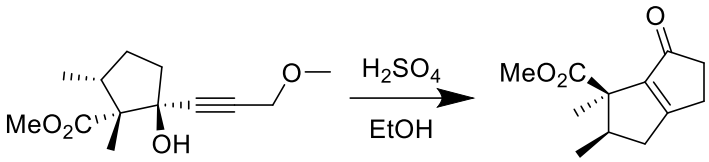
5.2.10



Note: Methyltriflate ($CF_3SO_2OCH_3$) reacts with water to form triflic acid (CF_3SO_2OH) and methanol.

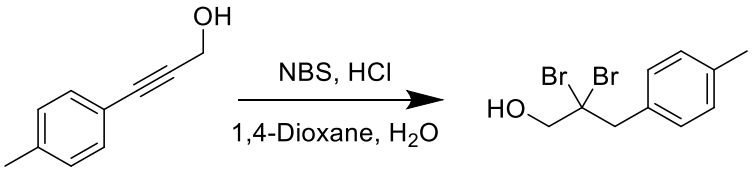
Wu, S.; Xu, X.; Tang, T.; Deng, X.; Zhang, S.; Yan, C.-G.; Zhang, J.; Wang, M.; Wang, L. Enantioselective Synthesis of Quaternary Stereocenter Aldehydes by Palladium-Catalyzed Intermolecular Propargylation Reaction. *J. Am. Chem. Soc.* 2026, *148* (15), 16058–16067. https://doi.org/10.1021/jacs.6c00417

5.2.11



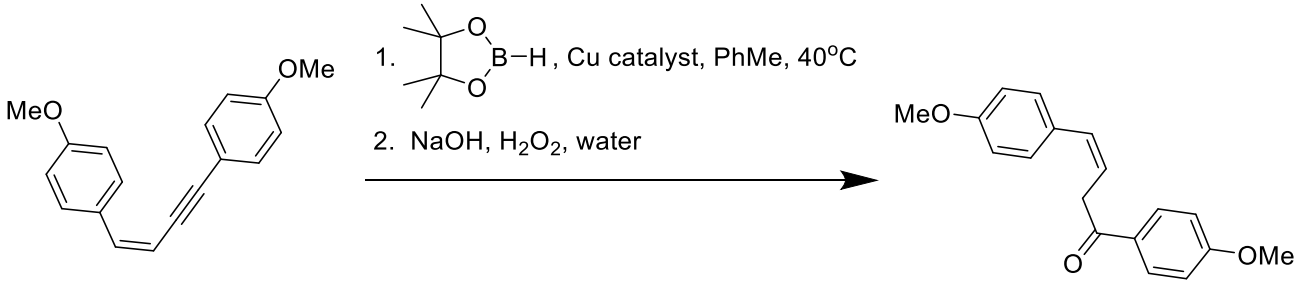
Goethe, O.; DiBello, M.; Herzon, S. B. Total Synthesis of Structurally Diverse Pleuromutilin Antibiotics. *Nat. Chem.* 2022, *14* (11), 1270-1277. https://doi.org/10.1038/s41557-022-01027-7

5.2.12



Chaisan, N.; Ruengsangtongkul, S.; Thongsornkleeb, C.; Tummatorn, J.; Ruchirawat, S. Dihalooxygenation of Alkynes and Alkynols: Preparation of 2,2-Dihaloketones and *gem*-Dihalolactols. *Synlett* 2022, *33* (14), 1426-1430. https://doi.org/10.1055/a-1774-7077

5.2.13



Buchbinder, N. W.; Nguyen, L. H.; Beck, O. N.; Bage, A. D.; Slebodnick, C.; Santos, W. L. Chemo-, Regio-, and Stereoselective cis-Hydroboration of 1,3-Enynes: Copper-Catalyzed Access to (Z,Z)- and (Z,E)-2-Boryl-1,3-dienes. *Org. Lett*. 2024, *26* (29), 6136–6141. https://doi.org/10.1021/acs.orglett

Section 6: Alcohols, Ethers, Thiols and Derivatives

Required foundation for this section: (some content maybe have been covered in other sections)

Synthesis of alcohols and ethers

Dehydration of alcohols via conversion to a halide and then dehydrohalogenation

Pinacol rearrangement

Oxidation of primary and secondary alcohols

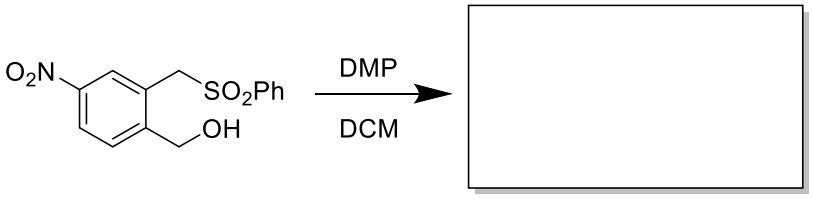
Alcohol protecting groups (silyl reagents)

Oxidation and reduction of sulfur-containing functional groups (reduction of thiols, oxidation of disulfides, oxidation of thioethers to sulfoxide and then sulfones.)

Section 6 – Box-Type Questions

For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

6.1.1



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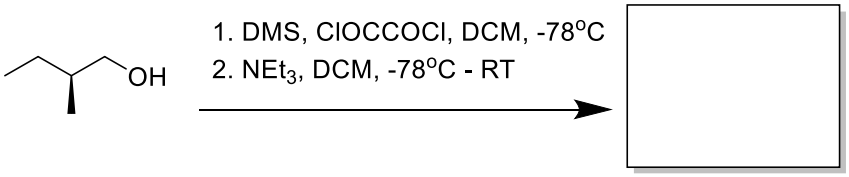

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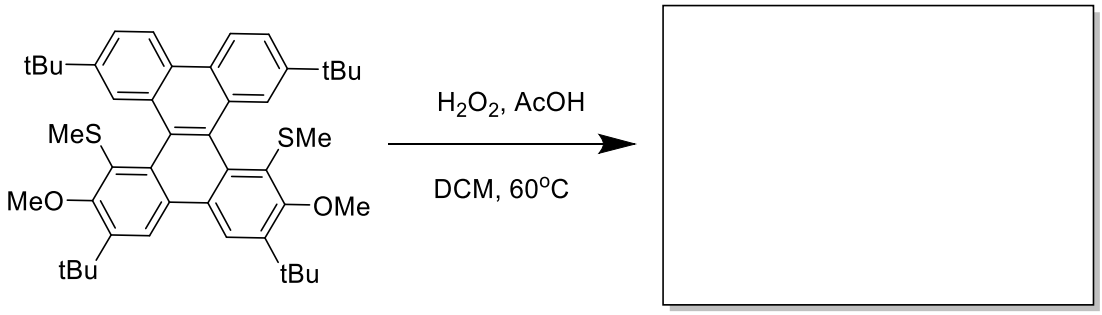

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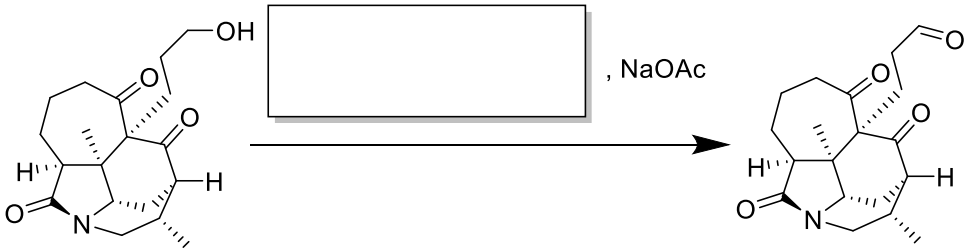

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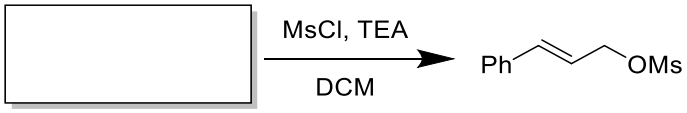

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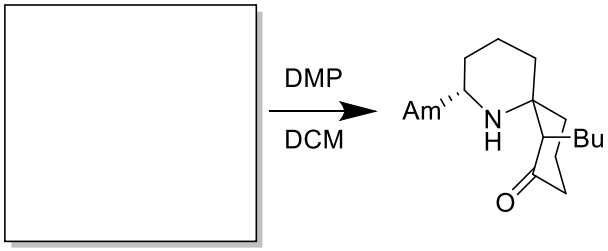

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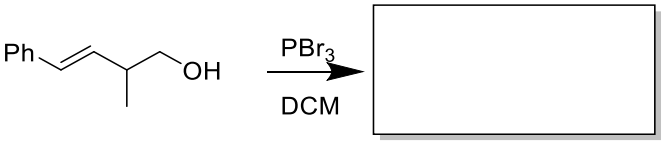

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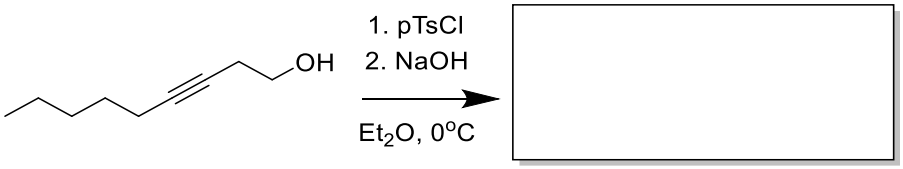

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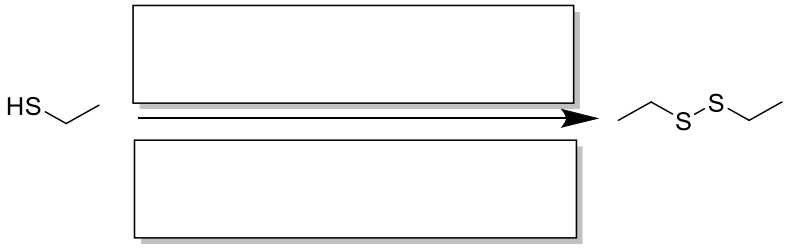

In introductory organic chemistry, common oxidants for thiols include air, bromine, and iodine in base. NBS can be viewed as a bromine equivalent and serves a similar oxidative function.

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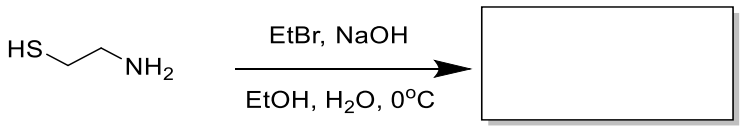

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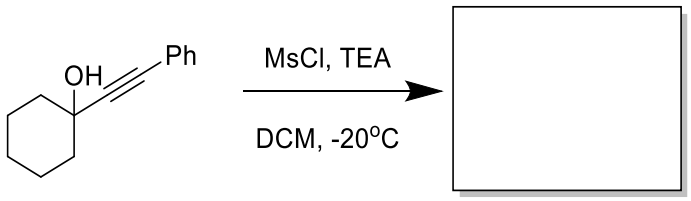

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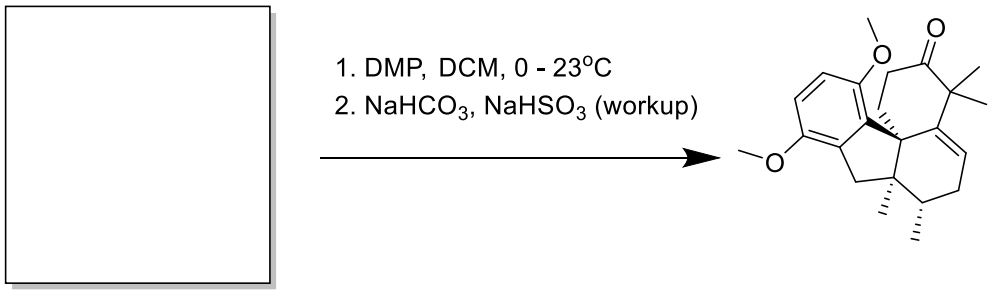

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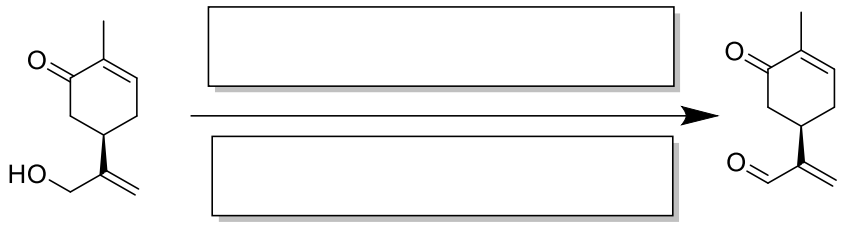

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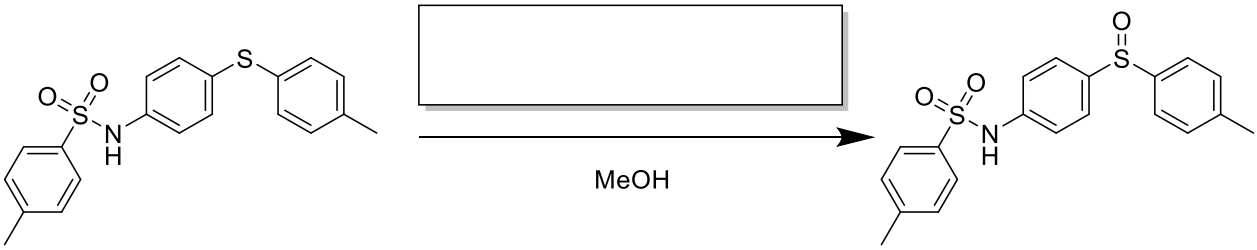

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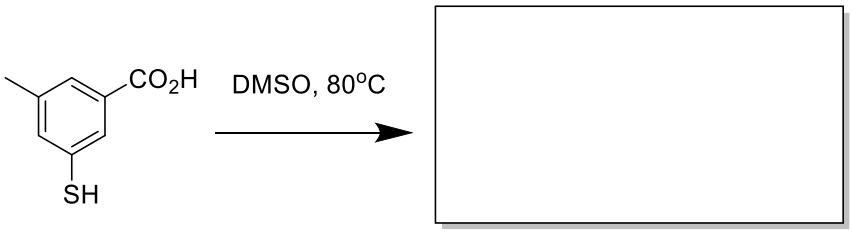

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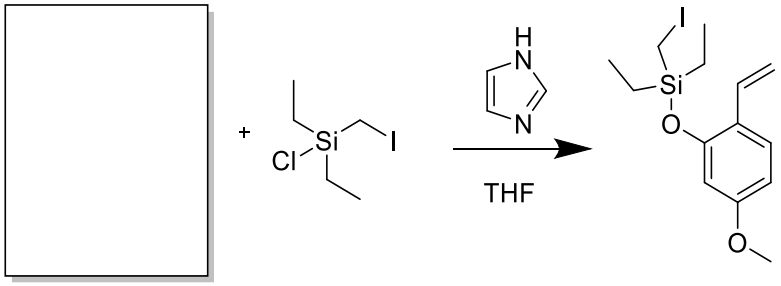

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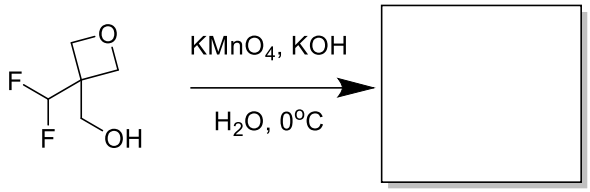

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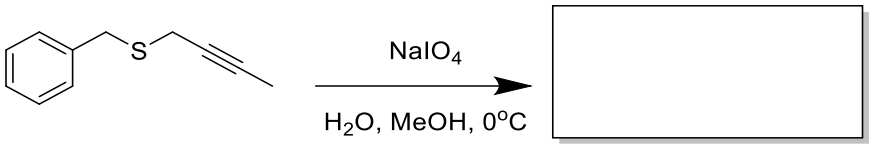

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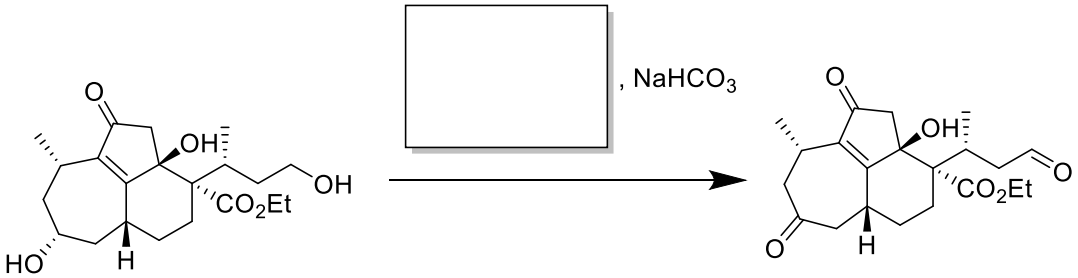

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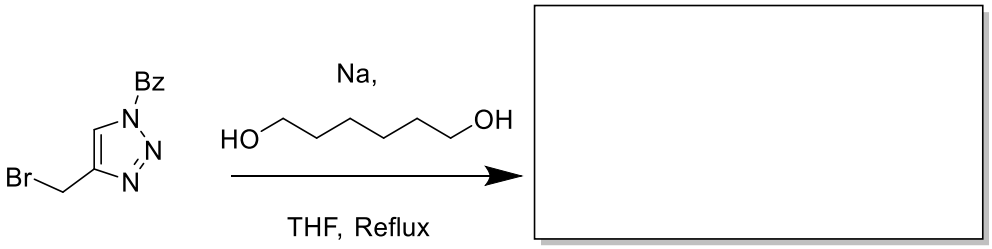

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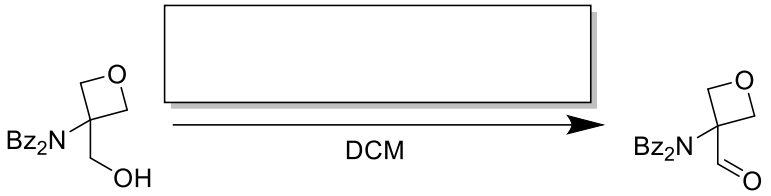

Litskan, E. V.; Lynnyk, S. V.; Shypov, R. H.; Vashchenko, B. V.; Hoida, A. Ye.; Klymenko-Ulianov, O. O.; Gorlova, A. O.; Granat, D. S.; Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V. Fine-Tuning of Physicochemical Properties of 3,3-Disubstituted Oxetanes Introducing Fluorine Atom(s) on the Building Blocks Level. *Chem. Eur. J.* 2025, *31* (51), e202500940. https://doi.org/10.1002/chem.202500940

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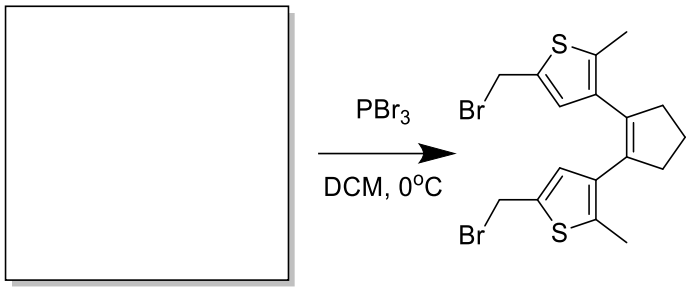

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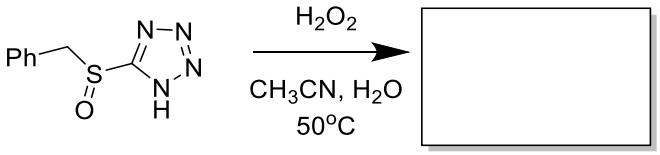

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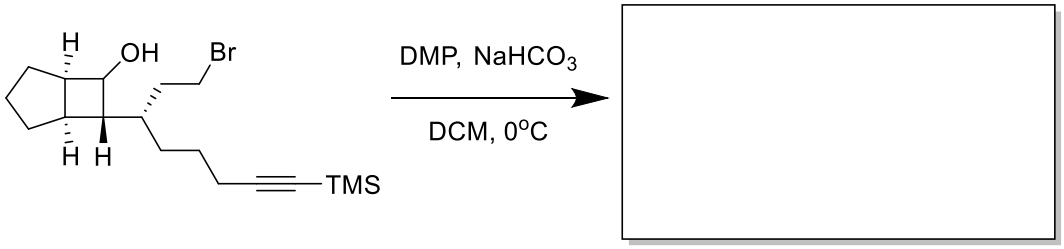

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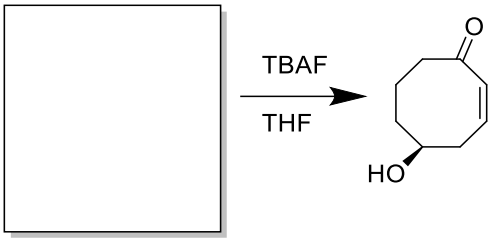

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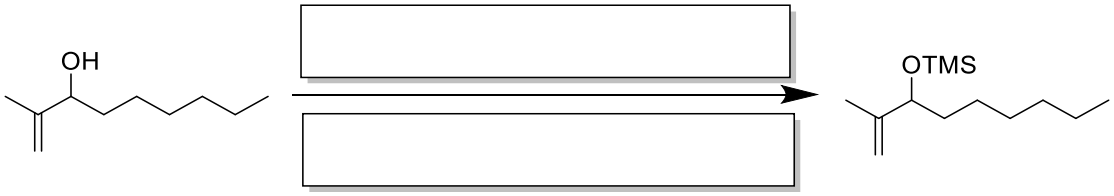

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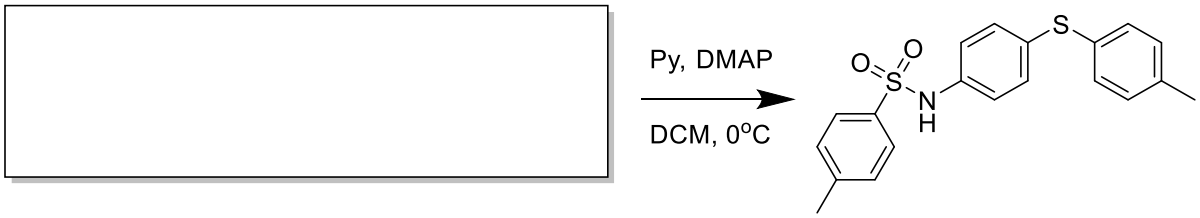

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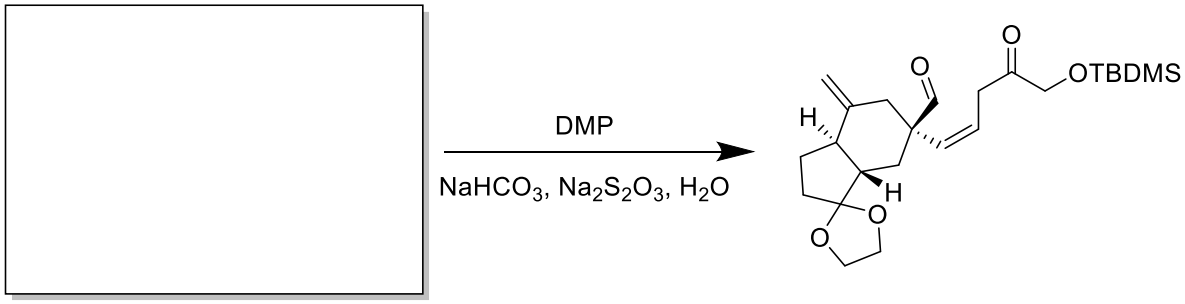

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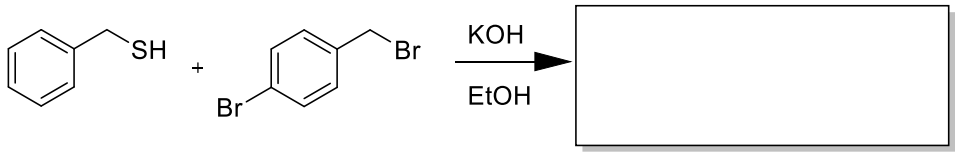

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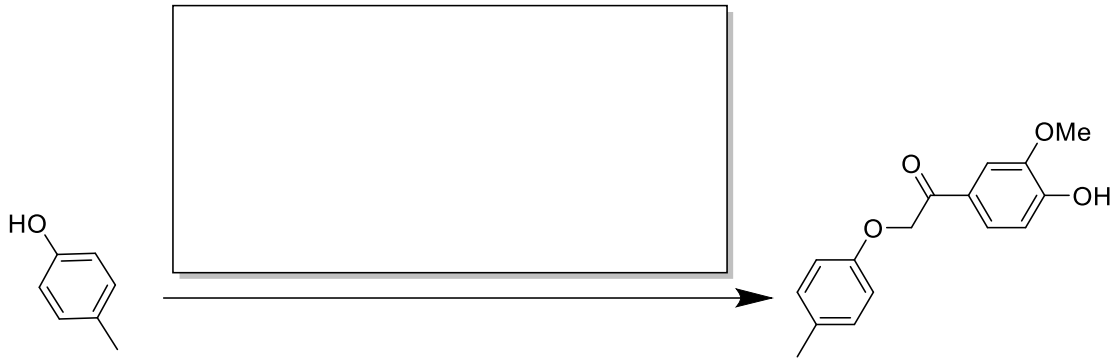

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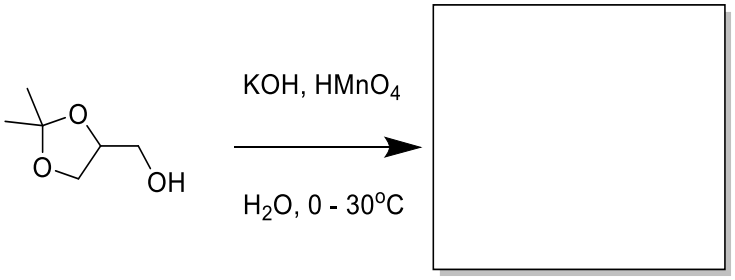

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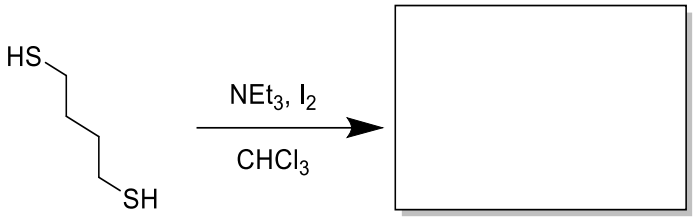
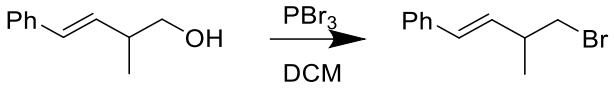


Bera, P.; Mukherjee, S.; Biswas, S. A Sustainable Pathway for CO2 Utilization: Pd(II)-Embedded Diamino-Functionalized Al(III) MOF Catalyst with High CO_2 Sorption Affinity Enabling Recyclable Synthesis of Bioactive Quinazolinones under Atmospheric Pressure Conditions. *Inorg. Chem.* 2026, *65* (33), 19495–19505. https://doi.org/10.1021/acs.inorgchem.6c02974

Section 6 – Mechanism Questions

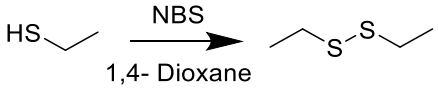
Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

6.2.1



Tsai, S.; Huang, Y.; Chou, C. Carboxylate-Directed Palladium-Catalyzed Regioselective Mizoroki-Heck Alkenylation of *γ* , *δ* -Unsaturated Carboxylic Acids. *Adv. Synth. Catal.* 2023, *365* (5), 699–703. https://doi.org/10.1002/adsc.202201317

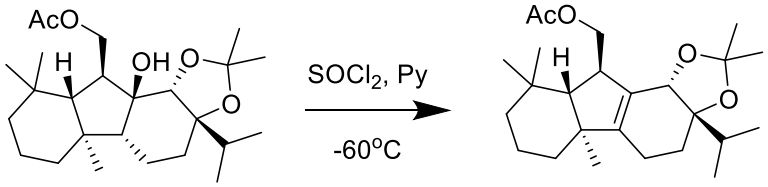
6.2.2



In introductory organic chemistry, common oxidants for thiols include air, bromine, and iodine in base. NBS can be viewed as a bromine equivalent and serves a similar oxidative function.

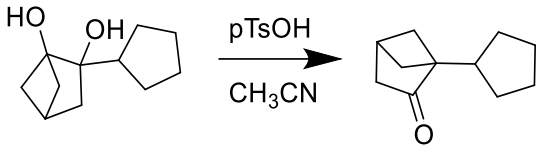
Yang, K.; Hu, Q.-Y.; Li, Q.; Liu, J.-X.; Li, Z.-Y.; Li, B.-J.; Sun, X.-Q. Metal-Free and NBS-Mediated Direct Thiol-Disulfide Exchange Reaction to Access Unsymmetrical Disulfides. *Eur. J. Org. Chem.* 2023, *26* (30), e202300394. https://doi.org/10.1002/ejoc.202300394

6.2.3



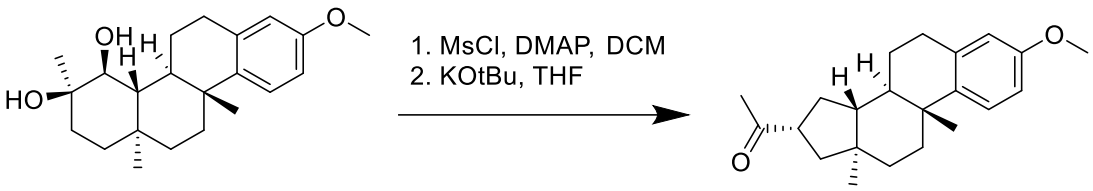
Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. Enantioselective Total Synthesis of Cytotoxic Taiwaniaquinones A and F. *Chem. Commun.* 2010, *46* (48), 9244. https://doi.org/10.1039/c0cc03763j

6.2.4



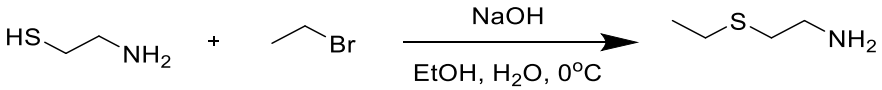
Lee, Y.-C.; Chen, Y.-C.; Wu, C.-F.; Yoo, W.-J. Synthesis of 1-Substituted Bicyclo[2.1.1]Hexan-2-Ones via a Sequential SmI_2 -Mediated Pinacol Coupling and Acid-Catalyzed Pinacol Rearrangement Reaction. *Org. Lett.* 2024, *26* (43), 9352–9356. https://doi.org/10.1021/acs.orglett.4c03541

6.2.5



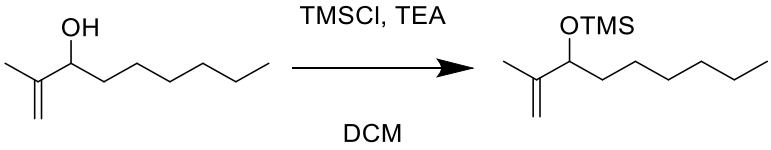
Stempel, Z. D.; Radomska, H. S.; Coss, C. C.; Micalizio, G. C. Function-Oriented Synthesis of Pentacyclic Triterpenoids and Discovery of an *Ent* -Estrane as a Natural Product-Inspired Androgen Receptor Antagonist. *Org. Lett.* 2024, *26* (15), 3054–3059. https://doi.org/10.1021/acs.orglett.4c00697

6.2.6



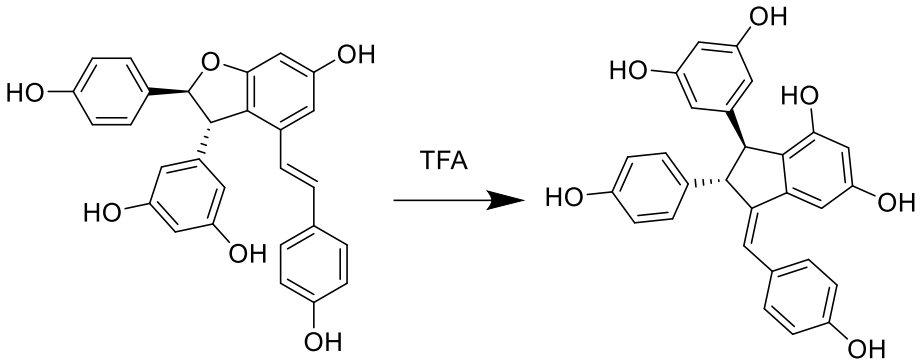
Wang, Z.; Lin, Q.; Ma, N.; Liu, S.; Han, M.; Yan, X.; Liu, Q.; Solan, G. A.; Sun, W.-H. Direct Synthesis of Ring-Fused Quinolines and Pyridines Catalyzed by NNHY-Ligated Manganese Complexes (Y = NR_2 or SR). *Catal. Sci. Technol.* 2021, *11* (24), 8026-8036. https://doi.org/10.1039/D1CY01945G

6.2.7



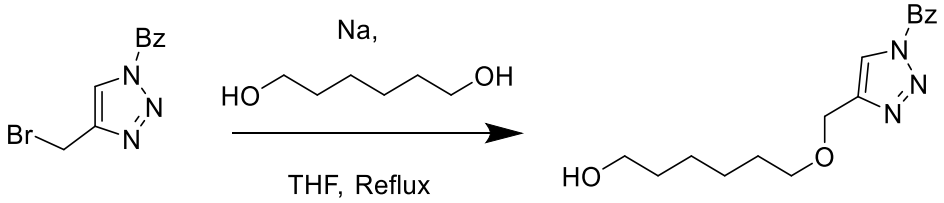
Han, Y.-F.; Hua, K.; Zhao, X.; Li, J.-H. Stereoselective Synthesis of (E)-Allylic Sulfones by Photocatalytic Desilyloxylative Sulfonylation of Allyl Silyl Ethers with Thiosulfonates. *Org. Lett.* 2026, *28* (18), 5698-5703. https://doi.org/10.1021/acs.orglett.6c01026

6.2.8



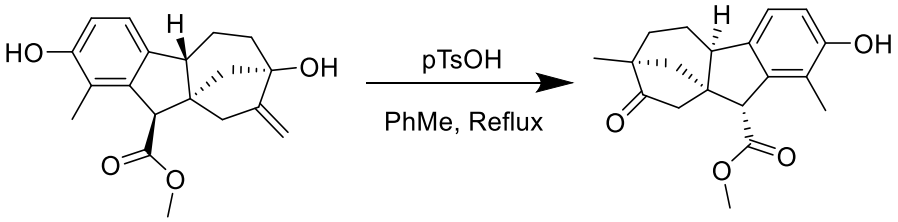
Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. Total Synthesis of Diverse Carbogenic Complexity within the Resveratrol Class from a Common Building Block. *J. Am. Chem. Soc.* 2009, *131* (5), 1753-1765. https://doi.org/10.1021/ja806183r

6.2.9



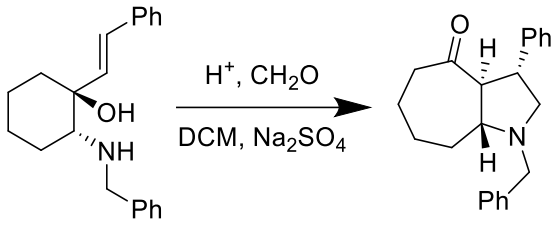
Huang, J.; Liu, S.; Ma, Y.; Cai, J. Chiral Salen Mn (III) Immobilized on ZnPS-PVPA through Alkoxyl-Triazole for Superior Performance Catalyst in Asymmetric Epoxidation of Unfunctionalized Olefins. *J. Organomet. Chem.* 2019, *886*, 27–33. https://doi.org/10.1016/j.jorganchem.2019.02.008

6.2.10



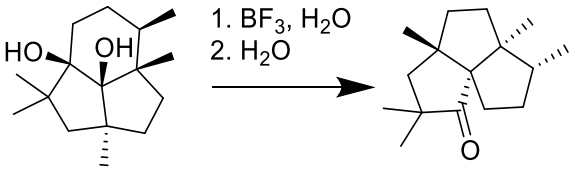
Annand, J. R.; Bruno, P. A.; Mapp, A. K.; Schindler, C. S. Synthesis and Biological Evaluation of Pharbinilic Acid and Derivatives as NF-κB Pathway Inhibitors. *Chem. Commun.* 2015, *51* (43), 8990–8993. https://doi.org/10.1039/C5CC02918J

6.2.11



Belov, D. S.; Lukyanenko, E. R.; Kurkin, A. V.; Yurovskaya, M. A. Highly Stereoselective and Scalable Synthesis of *Trans* -Fused Octahydrocyclohepta[*b*]Pyrrol-4(1 *H*)-Ones via the Aza-Cope–Mannich Rearrangement in Racemic and Enantiopure Forms. *J. Org. Chem.* 2012, *77* (22), 10125–10134. https://doi.org/10.1021/jo301762a

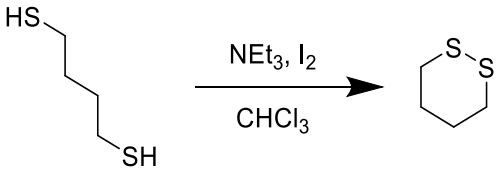
6.2.12



Hint: BF_3 is a Lewis acid.

Radulović, N. S.; Mladenović, M. Z.; Stojanović, N. M.; Randjelović, P. J.; Blagojević, P. D. Structural Elucidation of Presilphiperfolane-7α,8α-Diol, a Bioactive Sesquiterpenoid from *Pulicaria Vulgaris* : A Combined Approach of Solvent-Induced Chemical Shifts, GIAO Calculation of Chemical Shifts, and Full Spin Analysis. *J. Nat. Prod.* 2019, *82* (7), 1874–1885. https://doi.org/10.1021/acs.jnatprod.9b00120

6.2.13



Bera, P.; Mukherjee, S.; Biswas, S. A Sustainable Pathway for CO2 Utilization: Pd(II)-Embedded Diamino-Functionalized Al(III) MOF Catalyst with High CO_2 Sorption Affinity Enabling Recyclable Synthesis of Bioactive Quinazolinones under Atmospheric Pressure Conditions. *Inorg. Chem.* 2026, *65* (33), 19495–19505. https://doi.org/10.1021/acs.inorgchem.6c02974

Section 7: Aromatic Compounds

Required foundation for this section:

Electrophilic aromatic substitution

Nitration

Sulfonation

Halogenation

Friedel-Crafts alkylation and acylation

Reduction of nitro to aniline

Side-chain oxidation of alkylbenzenes

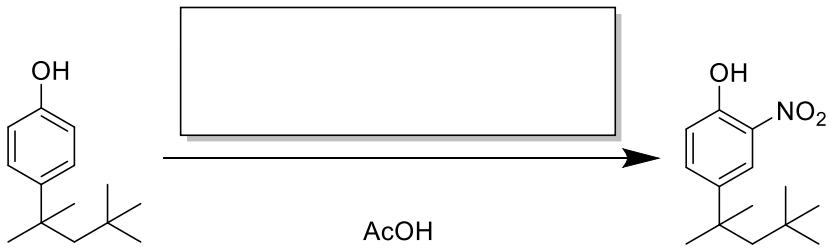
Benzylic bromination

Nucleophilic aromatic substitution

Section 7 – Box-Type Questions

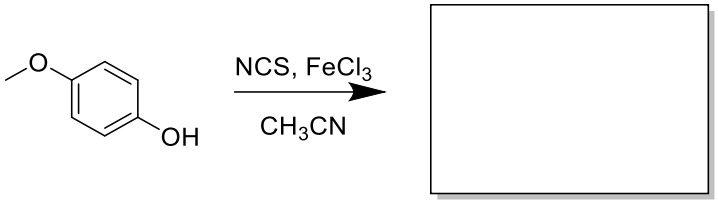
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

7.1.1



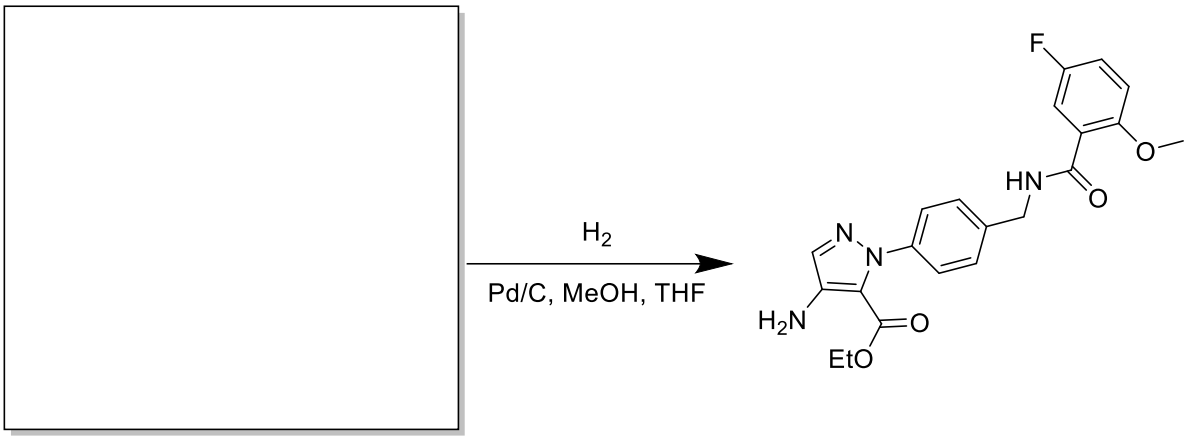
Wang, Y.-J.; Yang, X.-N.; Wang, F.; Wu, X.-F.; Shi, Y.-J.; Yang, Y.; Peng, X.-J.; Yi, H.; Li, K.; Yuan, J.; Li, Z.-R.; Gong, F.; Xue, S.-T. Design, Synthesis, and Antitumor Evaluation of Benzamide Derivatives Targeting HOXA1 Function. *J. Med. Chem.* **2026**, *69* (4), 4090-4111. https://doi.org/10.1021/acs.jmedchem.5c02745

7.1.2



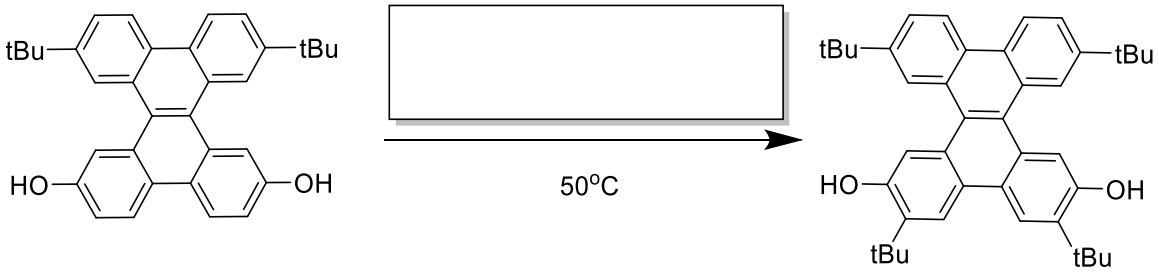
Shibuya, Y.; Nakagawa, N.; Miyagawa, N.; Suzuki, T.; Okano, K.; Mori, A. Unprecedented Regioregular Poly(1,4-arylene)s Prepared by Nickel(II)-Catalyzed Cross-Coupling Polymerization of 2,5-Disubstituted Bromo(chloro)arylene. *Angew. Chem. Int. Ed.* **2019**, *58* (28), 9547-9550. https://doi.org/10.1002/anie.201903791

7.1.3



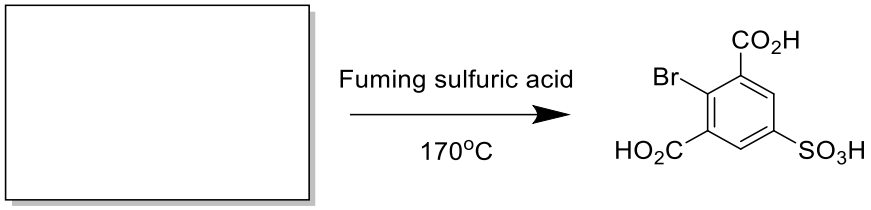
Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2026**, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

7.1.4



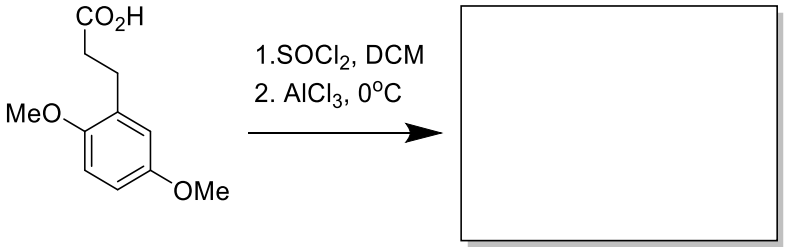
Yoshida, N.; Akasaka, R.; Yamaoka, Y.; Yashima, T.; Tokunaga, Y.; Iwasawa, T. Cross-Dimerization of Fluorenones for Synthesis of Dibenzo[*g,p*]chrysenes. *Tetrahedron* **2023**, *143*, 133549. https://doi.org/10.1016/j.tet.2023.133549

7.1.5



George, T. G.; Endeshaw, M. M.; Morgan, R. E.; Mahasenan, K. V.; Delfín, D. A.; Mukherjee, M. S.; Yakovich, A. J.; Fotie, J.; Li, C.; Werbovetz, K. A. Synthesis, Biological Evaluation, and Molecular Modeling of 3,5-Substituted-*N*1-Phenyl-*N*4,*N*4-di-*n*-butylsulfanilamides as Antikinetoplastid Antimicrotubule Agents. *Bioorg. Med. Chem.* **2007**, *15* (18), 6071-6079. https://doi.org/10.1016/j.bmc.2007.06.042

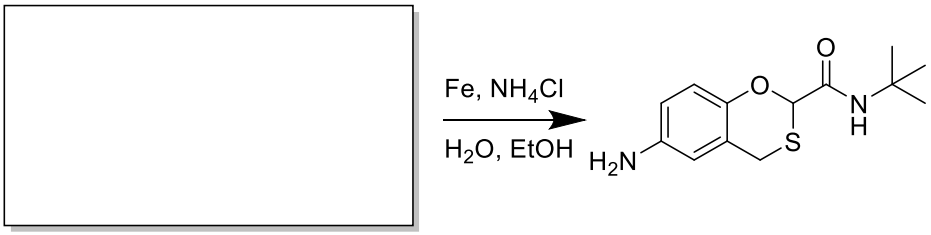
7.1.6



Note: $SOCl_2$ converts carboxylic acids into acid chlorides.

Gilbert, A.; Zuber, J.; Bach, T. Intramolecular *Ortho* Photocycloaddition of 4-Substituted 7-(4′-Alkenyloxy)-1-Indanones and Ensuing Reaction Cascades. *J. Org. Chem.* **2025**, *90* (11), 4099–4107. https://doi.org/10.1021/acs.joc.5c00171

7.1.7



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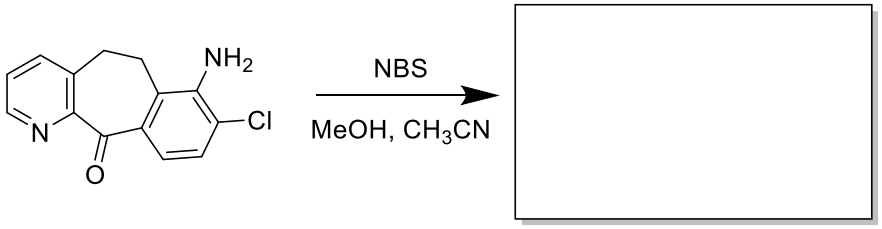
7.1.8



Fu, X.; McAllister, T. L.; Shi, X.; Thiruvengadam, T. K.; Tann, C.-H.; Lee, J. An Efficient One-Pot Process for 10-Bromo-8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, an Intermediate to SCH 66336. *Org. Process Res. Dev.* **2003**, *7* (5), 692-695. https://doi.org/10.1021/op034054f

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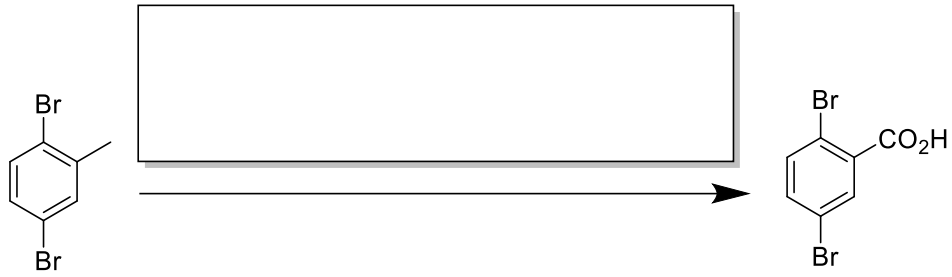

Chen, L.; Chen, Y.; Yao, K.; Zhou, W.; Li, F.; Chen, L.; Hu, R.; Tang, B. Z. A Novel Type of Optically Active Helical Liquid Crystalline Polymers: Synthesis and Characterization of Poly(*p*-phenylene)s Containing Terphenyl Mesogen with Different Terminal Groups. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47* (18), 4723-4735. https://doi.org/10.1002/pola.23526

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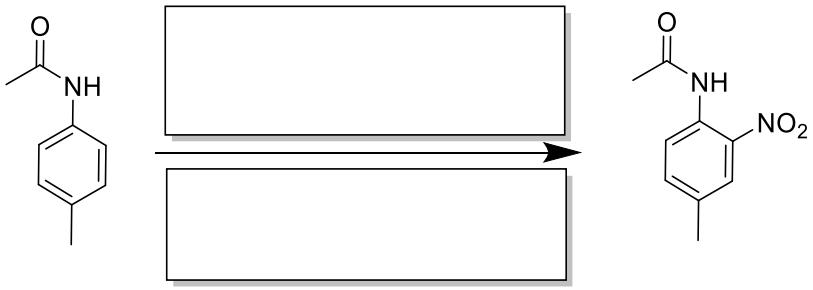
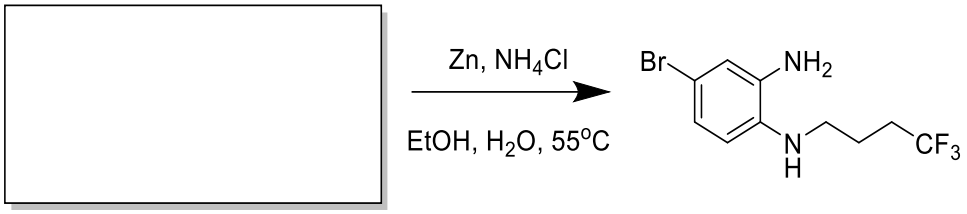


Glišić, B. Đ.; Hoffmann, M.; Warżajtis, B.; Genčić, M. S.; Blagojević, P. D.; Radulović, N. S.; Rychlewska, U.; Djuran, M. I. Selectivity of the Complexation Reactions of Four Regioisomeric Methylcamphorquinoxaline Ligands with Gold(III): X-Ray, NMR and DFT Investigations. *Polyhedron* **2016**, *105*, 137–149. https://doi.org/10.1016/j.poly.2015.12.009

7.1.11



Cao, T. D. C.; Neufeld, K.; Zarate, C.; Nichols, C. J.; Lellek, V.; Deidda, R.; Conza, M.; Schleiss, P.; Rinderhagen, H.; Pye, P.; Muuronen, M.; Chen, W.; Tona, V.; Jouffroy, L.; Viereck, P.; Matcha, K. An Expedient Synthetic Route to the Long-Acting RSV Inhibitor JNJ-6231 via Stereoselective Enzymatic Amination and Regioselective Alkylation. *Org. Process Res. Dev.* **2026**, *30* (1), 121-134. https://doi.org/10.1021/acs.oprd.5c00352

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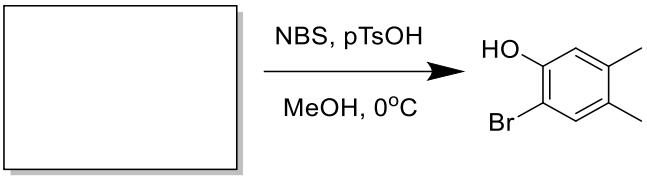

Stünkel, T.; Siebold, K.; Okumatsu, D.; Murata, K.; Ruyet, L.; Daniliuc, C. G.; Gilmour, R. *para*-Selective Dearomatization of Phenols by I(I)/I(III) Catalysis-Based Fluorination. *Chem. Sci.* **2023**, *14* (46), 13574-13580. https://doi.org/10.1039/D3SC05952A

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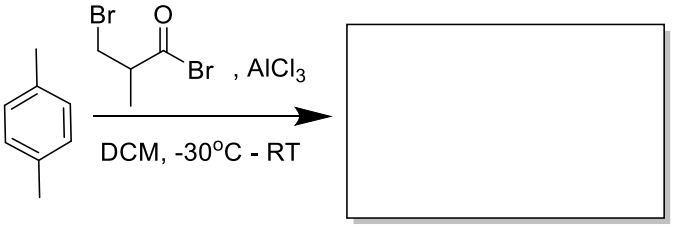
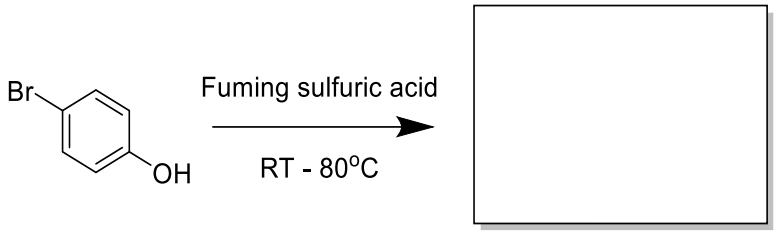


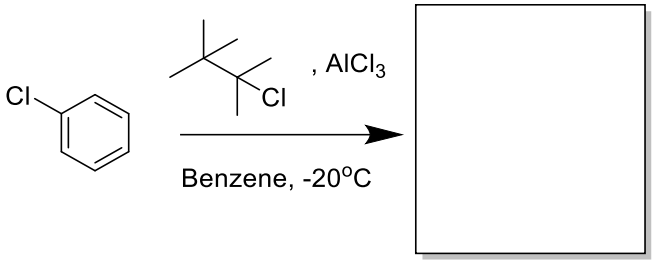
Kulyabin, P. S.; Sharikov, M. I.; Izmer, V. V.; Kononovich, D. S.; Goryunov, G. P.; Alexeev, N. V.; Uborsky, D. V.; Vittoria, A.; Antinucci, G.; Ehm, C.; Budzelaar, P. H. M.; Cipullo, R.; Busico, V.; Voskoboynikov, A. Z. Triptycene as a Scaffold in Metallocene Catalyzed Olefin Polymerization. *Dalton Trans.* **2024**, *53* (22), 9516-9525. https://doi.org/10.1039/D4DT01170H

7.1.14



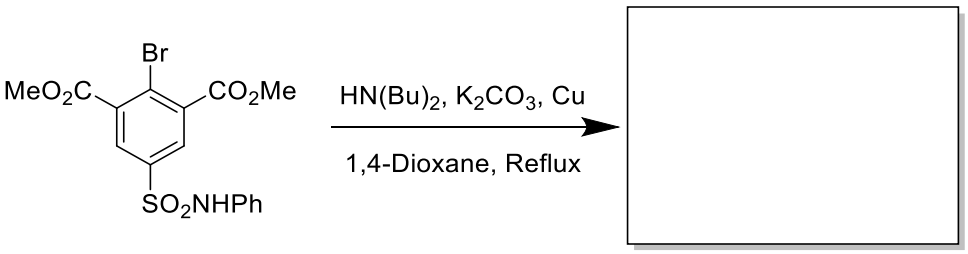
Deng, Z.-P.; Huo, L.-H.; Li, M.-S.; Zhang, L.-W.; Zhu, Z.-B.; Zhao, H.; Gao, S. Syntheses, Structures, and Luminescent Properties of Silver(I) Complexes Constructed from *ortho*-Hydroxyl Arenesulfonic Acids. *Cryst. Growth Des.* **2011**, *11* (7), 3090-3100. https://doi.org/10.1021/cg200360e

7.1.15



Yang, K.; He, S.; Huang, Y.; Xu, T.; Wang, Y.; Liu, K.; Zhang, L.; Ai, W.; Li, D.; Shen, T. Electrooxidative C-C Fragmentation of Aromatic Radical Cations for Cascade Benzylic Multifunctionalization. *Angew. Chem. Int. Ed.* **2026**, *65* (12), e22498. https://doi.org/10.1002/anie.202522498

7.1.16



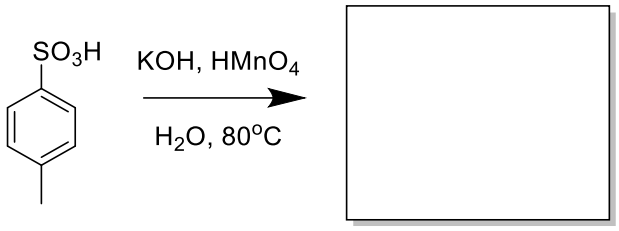
George, T. G.; Endeshaw, M. M.; Morgan, R. E.; Mahasenan, K. V.; Delfín, D. A.; Mukherjee, M. S.; Yakovich, A. J.; Fotie, J.; Li, C.; Werbovetz, K. A. Synthesis, Biological Evaluation, and Molecular Modeling of 3,5-Substituted-*N*1-Phenyl-*N*4,*N*4-di-*n*-butylsulfanilamides as Antikinetoplastid Antimicrotubule Agents. *Bioorg. Med. Chem.* **2007**, *15* (18), 6071-6079. https://doi.org/10.1016/j.bmc.2007.06.042

7.1.17



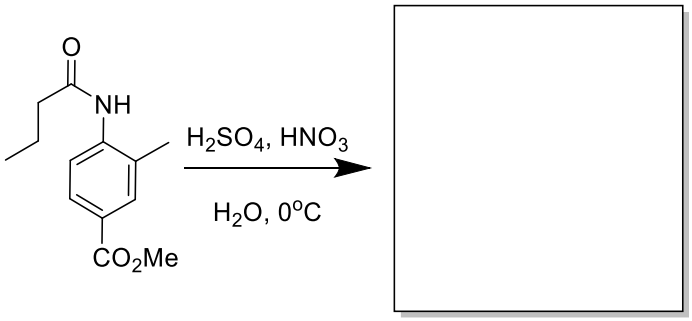
Li, J.; Yang, Y.; Cheng, L.; Xu, X.; Zhong, K.; Wang, T.; Chen, K.; Zhang, C.; He, C.; Xu, J.; Xu, S.; Luo, S. Discovery of 8-Quinolinesulfonamide Phenylimidazole-Based PKM2 Agonists for the Prevention and Delay of Aortic Dissection. *Eur. J. Med. Chem.* **2026**, *304*, 118479. https://doi.org/10.1016/j.ejmech.2025.118479

7.1.18



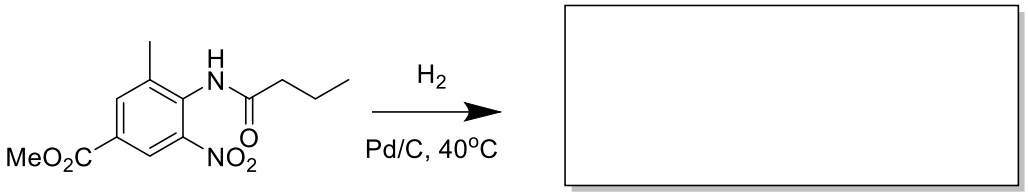
Huang, H.; Lu, W.; Li, X.; Cong, X.; Ma, H.; Liu, X.; Zhang, Y.; Che, P.; Ma, R.; Li, H.; Shen, X.; Jiang, H.; Huang, J.; Zhu, J. Design and Synthesis of Small Molecular Dual Inhibitor of Falcipain-2 and Dihydrofolate Reductase as Antimalarial Agent. *Bioorg. Med. Chem. Lett.* **2012**, *22* (2), 958-962. https://doi.org/10.1016/j.bmcl.2011.12.011

7.1.19



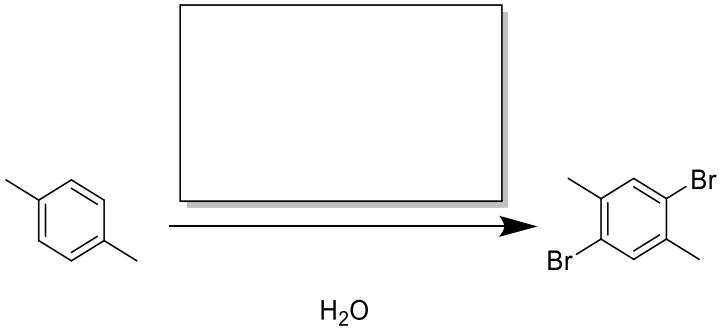
Zhang, Z.; Su, R.; Xiao, X.; Yang, J.; Zhang, G.; Wang, D.; Wang, S.; Wu, C. Efficient Synthesis of 1,7′-Dimethyl-2′-propyl-1H,3′H-2,5′-bibenzo[d]imidazole: Experiment, Crystal Structure, and DFT Calculations. *J. Mol. Struct.* **2026**, *1371*, 146521. https://doi.org/10.1016/j.molstruc.2026.146521

7.1.20



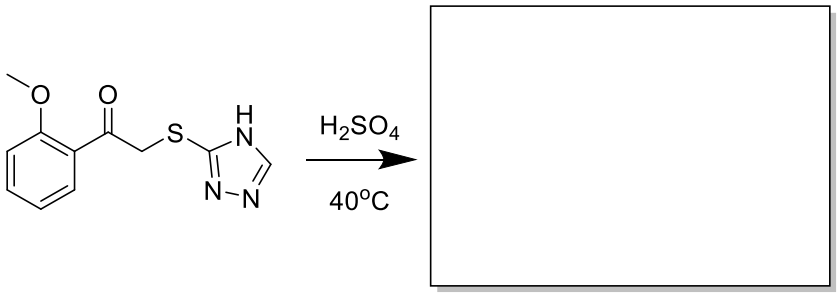
Zhang, Z.; Su, R.; Xiao, X.; Yang, J.; Zhang, G.; Wang, D.; Wang, S.; Wu, C. Efficient Synthesis of 1,7′-Dimethyl-2′-propyl-1H,3′H-2,5′-bibenzo[d]imidazole: Experiment, Crystal Structure, and DFT Calculations. *J. Mol. Struct.* **2026**, *1371*, 146521. https://doi.org/10.1016/j.molstruc.2026.146521

7.1.21



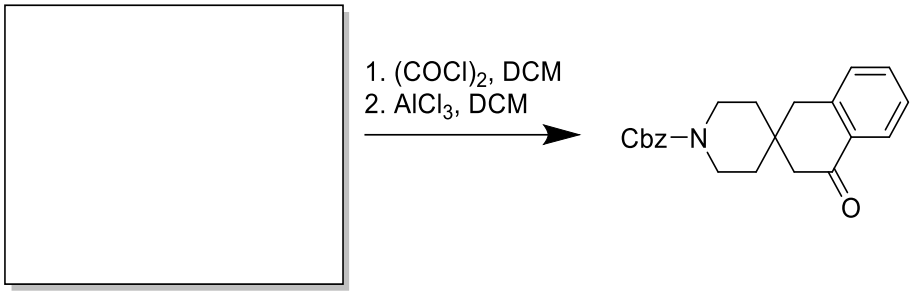
Fayoud, A.; Zorainy, M. Y. Selective Bromination of *p*-Xylene via Homogeneous Catalysis: Influence of Reaction Parameters on 2,5-Dibromo-*p*-Xylene Formation. *J. Phys.: Conf. Ser.* **2025**, *3051* (1), 012008. https://doi.org/10.1088/1742-6596/3051/1/012008

7.1.22



Krishnaraj, T.; Muthusubramanian, S. Synthesis of 6-Aryl-4*H*-imidazo[1,2-*b*][1,2,4]triazoles and 6-Aryl-thiazolo[3,2-*b*][1,2,4]triazoles. *J. Heterocycl. Chem.* **2015**, *52* (5), 1314-1320. https://doi.org/10.1002/jhet.2161

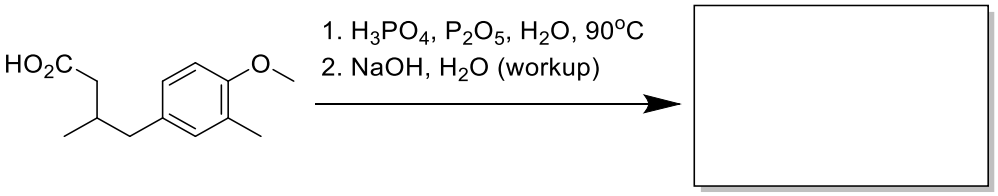
7.1.23



Note: $(COCl)_2$ is used to convert a carboxylic acid to an acid chloride.

Chu, G.-H.; Le Bourdonnec, B.; Gu, M.; Saeui, C. T.; Dolle, R. E. General and Efficient Synthetic Approach to Novel Tricyclic Spiroketones. *Tetrahedron* **2009**, *65* (27), 5161–5167. https://doi.org/10.1016/j.tet.2009.04.094

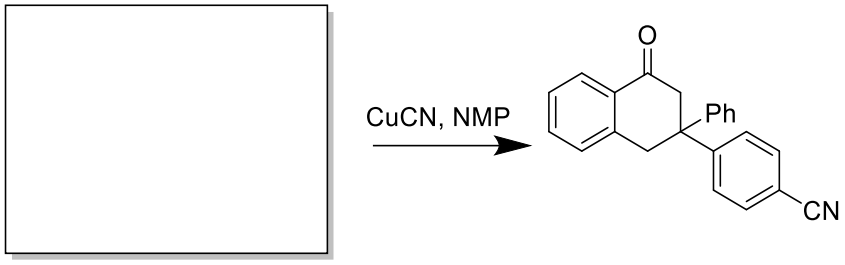
7.1.24



Hint: Step 1 is a strongly acidic condition.

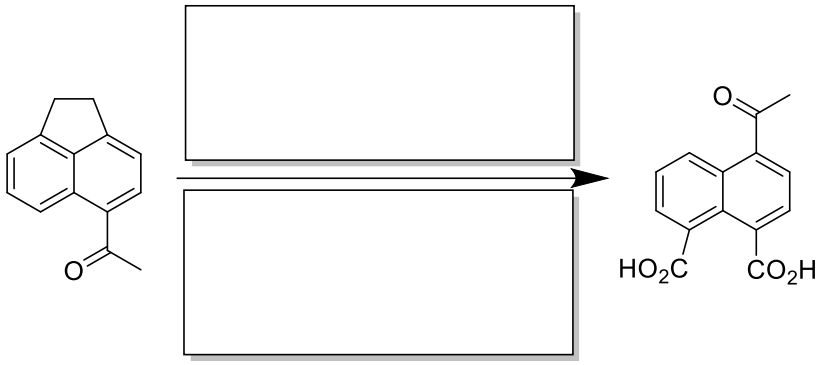
Roosen, P. C.; Karns, A. S.; Ellis, B. D.; Vanderwal, C. D. Evolution of a Short and Stereocontrolled Synthesis of (+)-7,20-Diisocyanoadociane. *J. Org. Chem.* **2022**, *87* (2), 1398–1420. https://doi.org/10.1021/acs.joc.1c02700

7.1.25



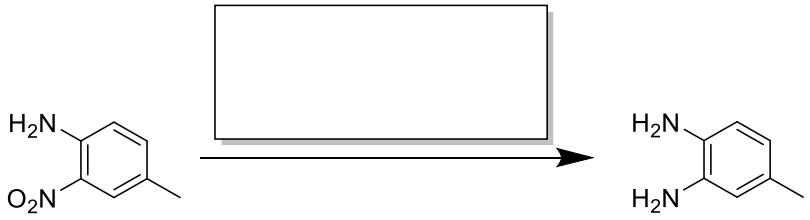
Zimmerman, H. E.; Suryanarayan, V. Organic Photochemical Rearrangements of Triplets and Zwitterions: Mechanistic and Exploratory Organic Photochemistry. *Eur. J. Org. Chem.* **2007**, *2007* (24), 4091-4102. https://doi.org/10.1002/ejoc.200700456

7.1.26



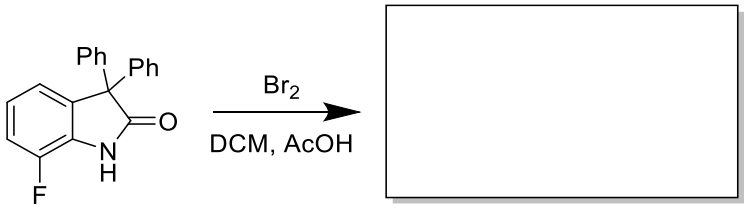
Dai, F.; Cao, Y.; Zhu, C.; Li, Y.; Ma, X.; Wang, S.; Liu, H.; Xie, X.; Gao, L.; Wang, Y.; Wang, C. Design, Synthesis, and Biological Evaluation of Naphthalimide-Polyamine Conjugate as a Potential Anti-Colorectal Cancer Agent. *Chem. Biodiversity* **2025**, *22* (4), e202401873. https://doi.org/10.1002/cbdv.202401873

7.1.27



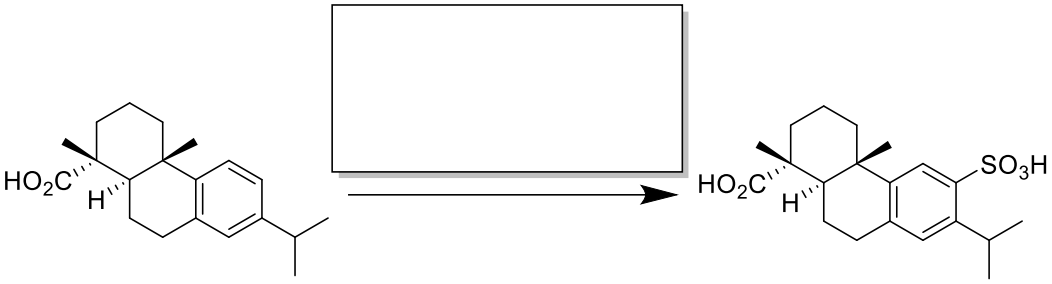
Glišić, B. Đ.; Hoffmann, M.; Warżajtis, B.; Genčić, M. S.; Blagojević, P. D.; Radulović, N. S.; Rychlewska, U.; Djuran, M. I. Selectivity of the Complexation Reactions of Four Regioisomeric Methylcamphorquinoxaline Ligands with Gold(III): X-Ray, NMR and DFT Investigations. *Polyhedron* **2016**, *105*, 137–149. https://doi.org/10.1016/j.poly.2015.12.009

7.1.28



Lamba, M.; Kumar, M.; Mane, M. V.; Goswami, A. Selectfluor-Mediated Directing Group and Transition Metal Catalyst-Free Site-Selective C7 Fluorination of 2-Oxindoles. *Adv. Synth. Catal.* **2026**, *368* (12), e70538. https://doi.org/10.1002/adsc.70538

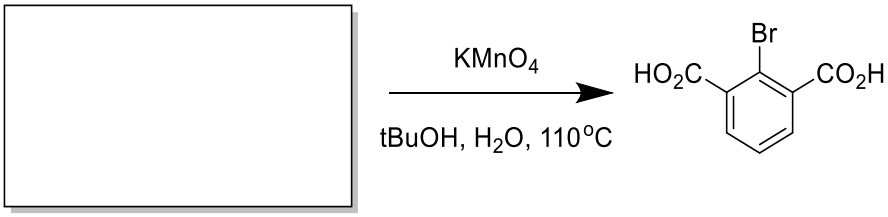
7.1.29



Note: The authors conducted this experiment at room temperature.

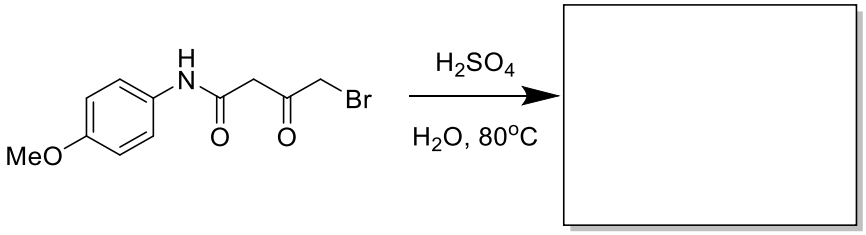
Huang, R.-Z.; Liang, G.-B.; Huang, X.-C.; Zhang, B.; Zhou, M.-M.; Liao, Z.-X.; Wang, H.-S. Discovery of Dehydroabietic Acid Sulfonamide Based Derivatives as Selective Matrix Metalloproteinases Inactivators That Inhibit Cell Migration and Proliferation. *Eur. J. Med. Chem.* **2017**, *138*, 979-992. https://doi.org/10.1016/j.ejmech.2017.07.020

7.1.30



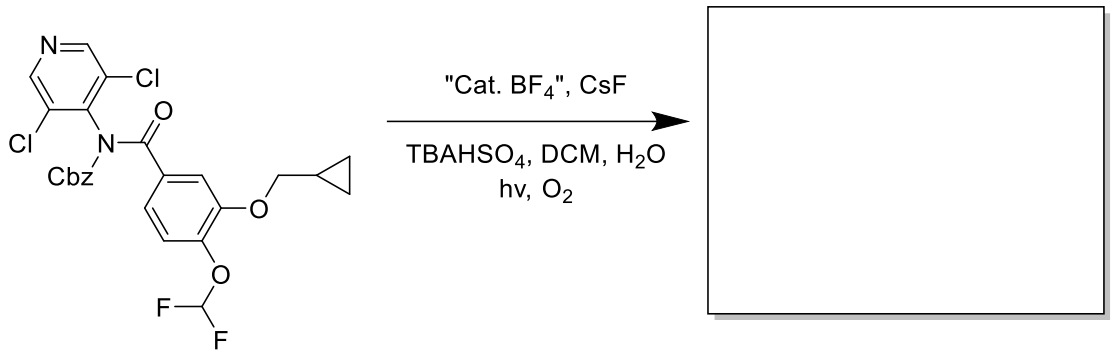
Narayanan, D.; Tran, K. T.; Pallesen, J. S.; Solbak, S. M. Ø.; Qin, Y.; Mukminova, E.; Luchini, M.; Vasilyeva, K. O.; González Chichón, D.; Goutsiou, G.; Poulsen, C.; Haapanen, N.; Popowicz, G. M.; Sattler, M.; Olagnier, D.; Gajhede, M.; Bach, A. Development of Noncovalent Small-Molecule Keap1-Nrf2 Inhibitors by Fragment-Based Drug Discovery. *J. Med. Chem.* **2022**, *65* (21), 14481–14526. https://doi.org/10.1021/acs.jmedchem.2c00830

7.1.31



Pan, G.; Qin, S.; Xu, D.; Kühn, F. E.; Guo, H. Visible Light-Induced Pericyclic Cascade Reaction for the Synthesis of Quinolinone Derivatives with an Oxabicyclo[4.2.0]octene Skeleton. *Org. Lett.* **2021**, *23* (8), 2959-2963. https://doi.org/10.1021/acs.orglett.1c00642

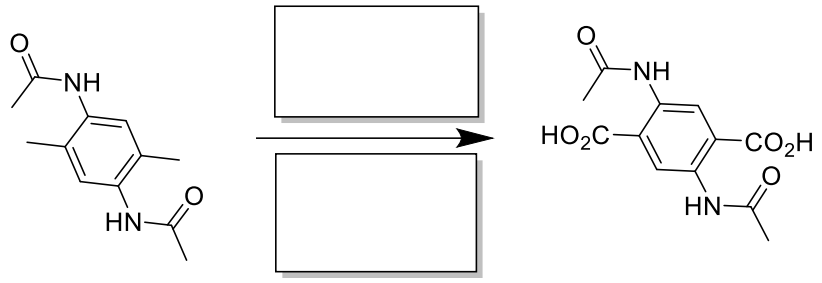
7.1.32



Note: For an introductory organic chemistry course, just focus on the CsF and the reactant.

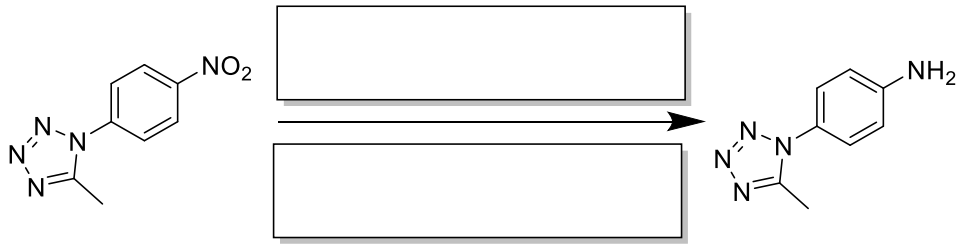
Mungalpara, M. N.; Wu, X.; Ma, X.; Zhu, Z.; Jiang, M.; Pike, V. W.; Lu, S.; Zhang, H.; Wu, Z.; Kinon, P. O.; Huang, Y.; Nicewicz, D. A.; Li, Z. Deoxyradiofluorination of Phenols via a Difluoromethoxy Nucleofuge Enabled by Organic Photoredox Catalysis. *ACS Cent. Sci.* **2026**, *12* (5), 638-648. https://doi.org/10.1021/acscentsci.6c00127

7.1.33



Bera, P.; Mukherjee, S.; Biswas, S. A Sustainable Pathway for CO2 Utilization: Pd(II)-Embedded Diamino-Functionalized Al(III) MOF Catalyst with High CO2 Sorption Affinity Enabling Recyclable Synthesis of Bioactive Quinazolinones under Atmospheric Pressure Conditions. *Inorg. Chem.* **2026**, *65* (33), 19495–19505. https://doi.org/10.1021/acs.inorgchem.6c02974

7.1.34



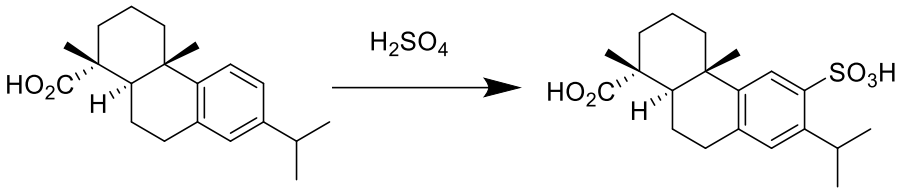
Learners in introductory organic chemistry typically learn to reduce the nitro group with tin or iron in acid or using catalytic hydrogenation and therefore may not propose what the authors used.

Sulakhe, S. M.; Khanzode, A. K.; Jamale, S. E.; Singh, M. B.; Singh, P.; Kumari, J.; Sriram, D.; Vedpathak, S. G.; Haval, K. P. New Benzofuran-Triazole-Tetrazole Conjugates: Synthesis, Antitubercular Evaluation, Molecular Docking, DFT, and MD Simulation. *J. Mol. Struct*. **2027**, *1379*, 147348. https://doi.org/10.1016/j.molstruc.2026.147348

Section 7 – Mechanism Questions

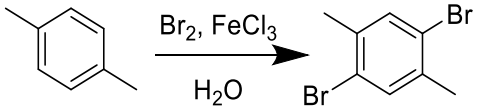
Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

7.2.1



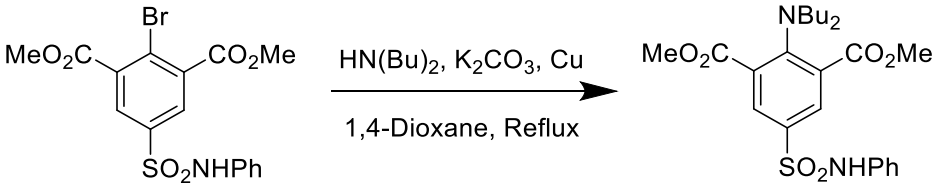
Huang, R.-Z.; Liang, G.-B.; Huang, X.-C.; Zhang, B.; Zhou, M.-M.; Liao, Z.-X.; Wang, H.-S. Discovery of Dehydroabietic Acid Sulfonamide Based Derivatives as Selective Matrix Metalloproteinases Inactivators That Inhibit Cell Migration and Proliferation. *Eur. J. Med. Chem.* **2017**, *138*, 979-992. https://doi.org/10.1016/j.ejmech.2017.07.020

7.2.2



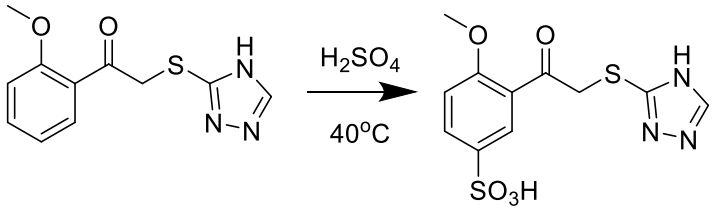
Fayoud, A.; Zorainy, M. Y. Selective Bromination of *p*-Xylene via Homogeneous Catalysis: Influence of Reaction Parameters on 2,5-Dibromo-*p*-Xylene Formation. *J. Phys.: Conf. Ser.* **2025**, *3051* (1), 012008. https://doi.org/10.1088/1742-6596/3051/1/012008

7.2.3



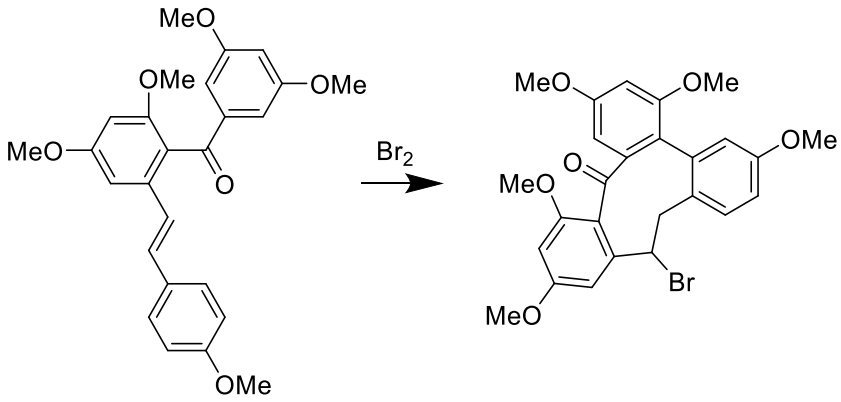
George, T. G.; Endeshaw, M. M.; Morgan, R. E.; Mahasenan, K. V.; Delfín, D. A.; Mukherjee, M. S.; Yakovich, A. J.; Fotie, J.; Li, C.; Werbovetz, K. A. Synthesis, Biological Evaluation, and Molecular Modeling of 3,5-Substituted-*N*1-Phenyl-*N*4,*N*4-di-*n*-butylsulfanilamides as Antikinetoplastid Antimicrotubule Agents. *Bioorg. Med. Chem.* **2007**, *15* (18), 6071-6079. https://doi.org/10.1016/j.bmc.2007.06.042

7.2.4



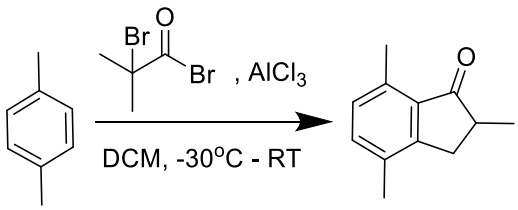
Krishnaraj, T.; Muthusubramanian, S. Synthesis of 6-Aryl-4*H*-imidazo[1,2-*b*][1,2,4]triazoles and 6-Aryl-thiazolo[3,2-*b*][1,2,4]triazoles. *J. Heterocycl. Chem.* **2015**, *52* (5), 1314-1320. https://doi.org/10.1002/jhet.2161

7.2.5



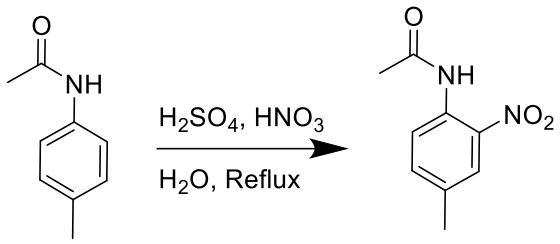
Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. Total Synthesis of Diverse Carbogenic Complexity within the Resveratrol Class from a Common Building Block. *J. Am. Chem. Soc.* **2009**, *131* (5), 1753–1765. https://doi.org/10.1021/ja806183r

7.2.6



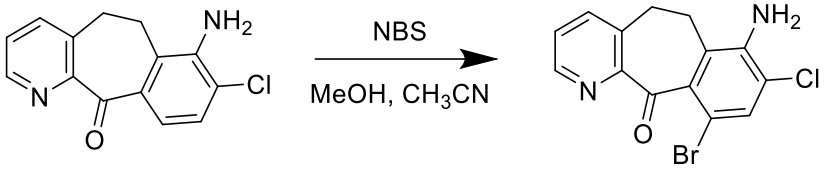
Kulyabin, P. S.; Sharikov, M. I.; Izmer, V. V.; Kononovich, D. S.; Goryunov, G. P.; Alexeev, N. V.; Uborsky, D. V.; Vittoria, A.; Antinucci, G.; Ehm, C.; Budzelaar, P. H. M.; Cipullo, R.; Busico, V.; Voskoboynikov, A. Z. Triptycene as a Scaffold in Metallocene Catalyzed Olefin Polymerization. *Dalton Trans.* **2024**, *53* (22), 9516-9525. https://doi.org/10.1039/D4DT01170H

7.2.7



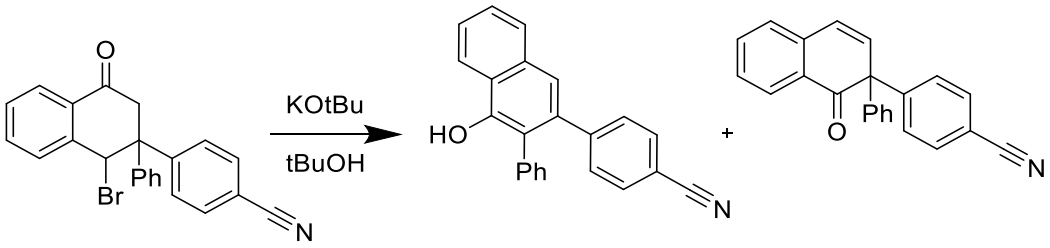
Glišić, B. Đ.; Hoffmann, M.; Warżajtis, B.; Genčić, M. S.; Blagojević, P. D.; Radulović, N. S.; Rychlewska, U.; Djuran, M. I. Selectivity of the Complexation Reactions of Four Regioisomeric Methylcamphorquinoxaline Ligands with Gold(III): X-Ray, NMR and DFT Investigations. *Polyhedron* **2016**, *105*, 137–149. https://doi.org/10.1016/j.poly.2015.12.009

7.2.8



Fu, X.; McAllister, T. L.; Shi, X.; Thiruvengadam, T. K.; Tann, C.-H.; Lee, J. An Efficient One-Pot Process for 10-Bromo-8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, an Intermediate to SCH 66336. *Org. Process Res. Dev.* **2003**, *7* (5), 692-695. https://doi.org/10.1021/op034054f

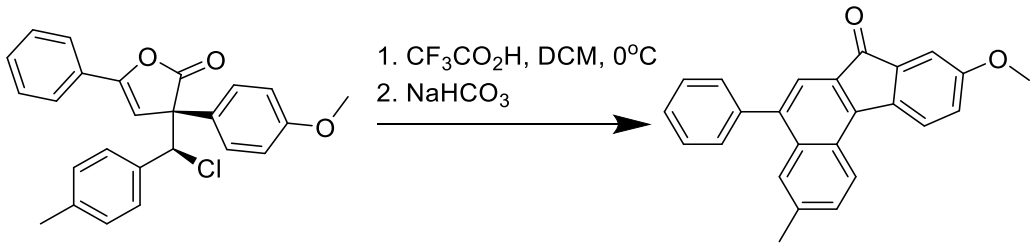
7.2.9



Show the reaction mechanism for both products. Hint: A cyclopropane ring intermediate is proposed.

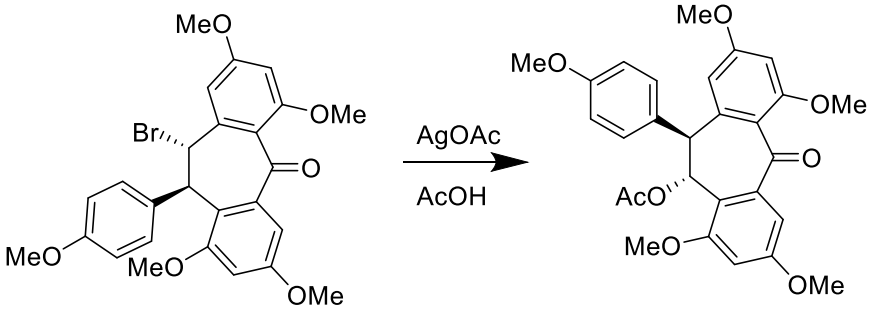
Zimmerman, H. E.; Suryanarayan, V. Organic Photochemical Rearrangements of Triplets and Zwitterions: Mechanistic and Exploratory Organic Photochemistry. *Eur. J. Org. Chem.* **2007**, *2007* (24), 4091-4102. https://doi.org/10.1002/ejoc.200700456

7.2.10



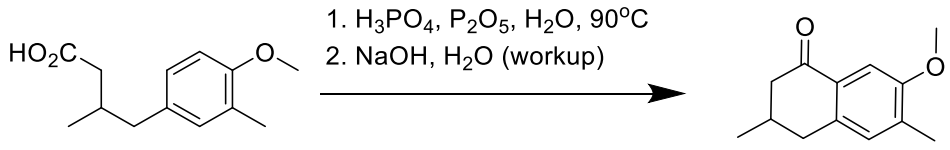
Lei, S.; Bu, S.; Yao, M.; Wang, S. R. Divergent Aromatization of α-Halobenzyl γ-Butenolides Initiated by Selective Enol Protonation to Benzo[*c*]fluorenones and Naphthalenes. *J. Org. Chem.* **2024**, *89* (15), 11067-11071. https://doi.org/10.1021/acs.joc.4c01181

7.2.11



Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. Total Synthesis of Diverse Carbogenic Complexity within the Resveratrol Class from a Common Building Block. *J. Am. Chem. Soc.* **2009**, *131* (5), 1753-1765. https://doi.org/10.1021/ja806183r

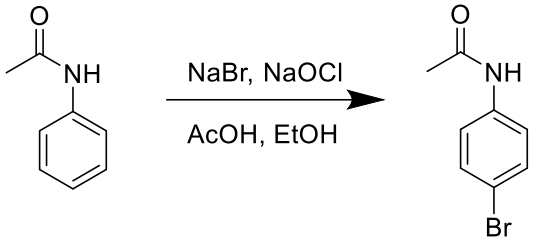
7.2.12



Hint: Step 1 is a strongly acidic condition.

Roosen, P. C.; Karns, A. S.; Ellis, B. D.; Vanderwal, C. D. Evolution of a Short and Stereocontrolled Synthesis of (+)-7,20-Diisocyanoadociane. *J. Org. Chem.* **2022**, *87* (2), 1398–1420. https://doi.org/10.1021/acs.joc.1c02700

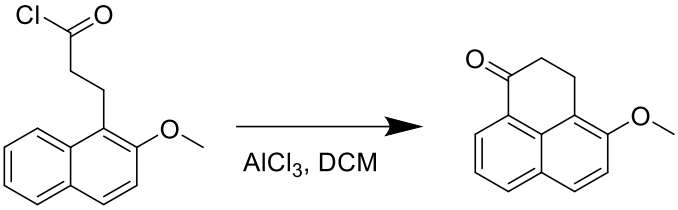
7.2.13



Note: The reagents produce molecular bromine.

Cardinal, P.; Greer, B., Luong, H.; Tyagunova, Y. A Multistep Synthesis Incorporating a Green Bromination of an Aromatic Ring. *J. Chem. Educ*. **2012**; *89* (8): 1061–1063. https://doi.org/10.1021/ed200579w

7.2.14



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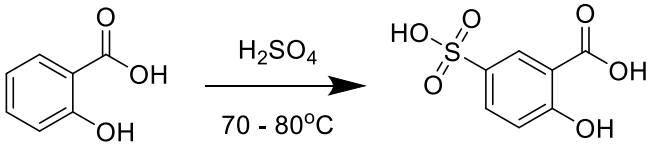
7.2.15



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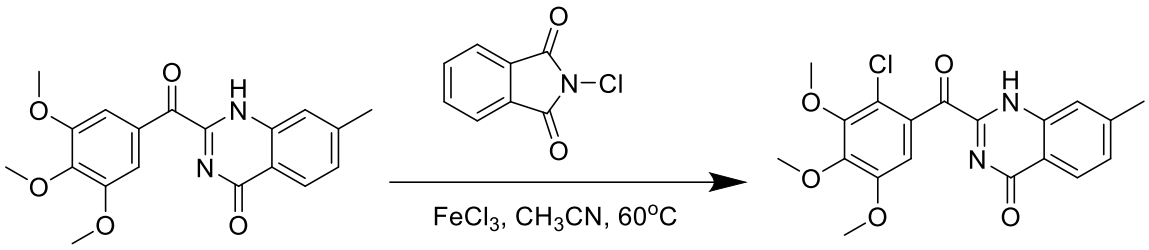
7.2.16



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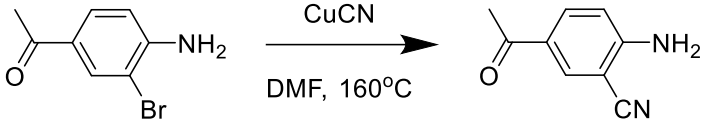
7.2.17



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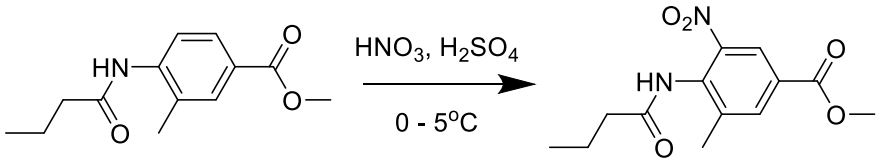


Zhang, Z.; Su, R.; Xiao, X.; Yang, J.; Zhang, G.; Wang, D.; Wang, S.; Wu, C. Efficient Synthesis of 1,7′-Dimethyl-2′-propyl-1H,3′H-2,5′-bibenzo[d]imidazole: Experiment, Crystal Structure, and DFT Calculations. *J. Mol. Struct*. **2026**, *1371*, 146521. https://doi.org/10.1016/j.molstruc.2026.146521

Section 8a: Aldehydes and Ketones 1

Required foundation for this section:

Nucleophilic addition

Hydride reduction to alcohols (including hydroboration of carbonyls)

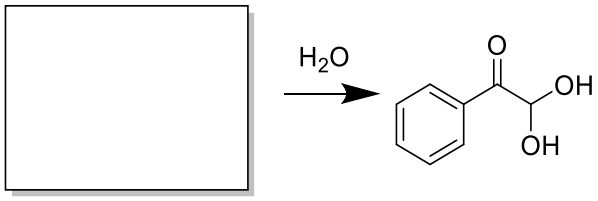
Grignard reagents

Acetal/ketal/thioacetals formation

Section 8a – Box-Type Questions

For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

8a.1.1



Note: The authors did not need to add an acid catalyst for the reaction to work.

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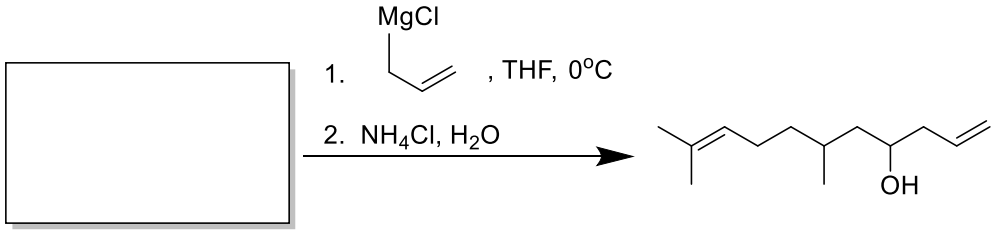

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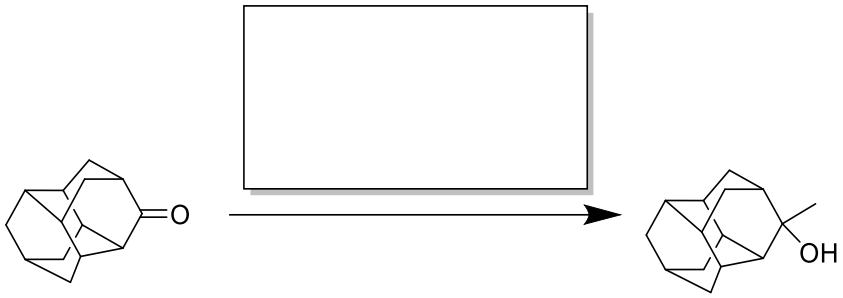

Fokin, A. A.; Zhuk, T. S.; Pashenko, A. E.; Dral, P. O.; Gunchenko, P. A.; Dahl, J. E. P.; Carlson, R. M. K.; Koso, T. V.; Serafin, M.; Schreiner, P. R. Oxygen-Doped Nanodiamonds: Synthesis and Functionalizations. *Org. Lett.* **2009**, *11* (14), 3068–3071. https://doi.org/10.1021/ol901089h

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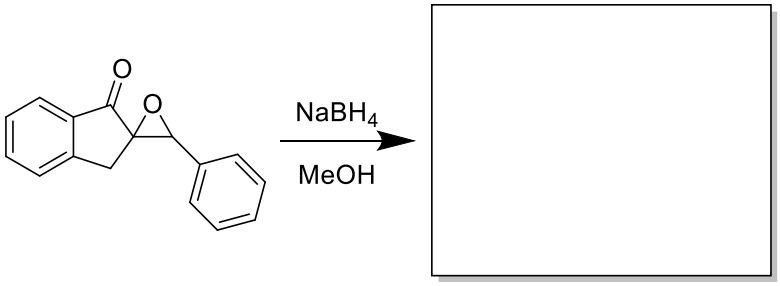

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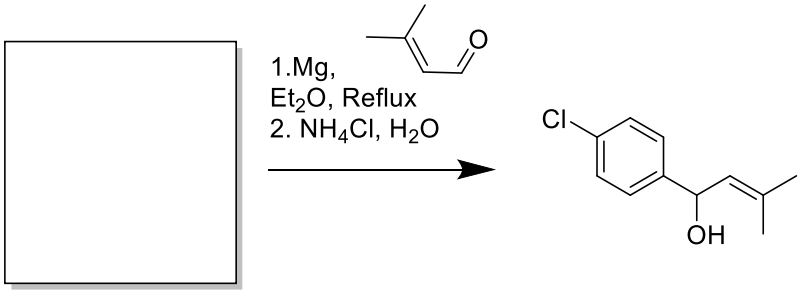

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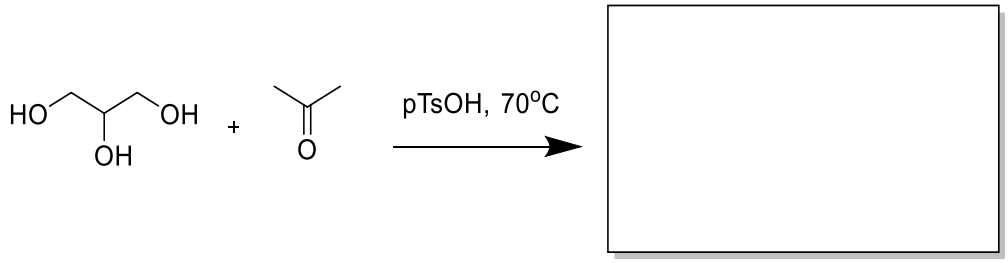

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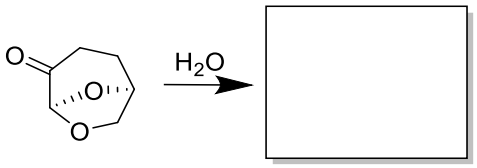

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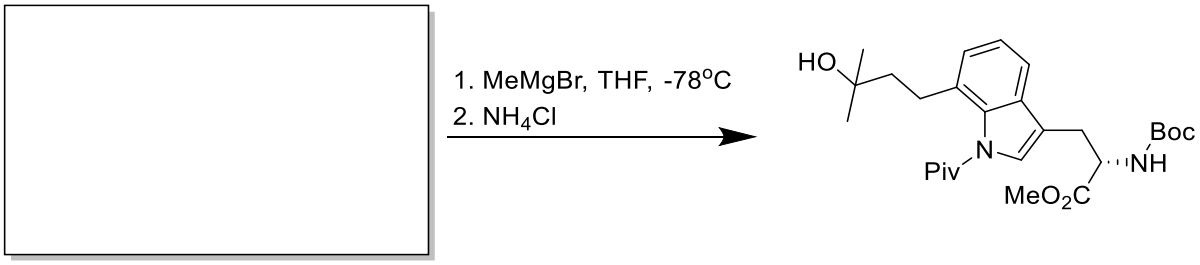

Devarajappa, R.; Hanessian, S. Total Synthesis of Asperdinones B, C, D, E and Terezine D. *Beilstein J. Org. Chem.* **2025**, *21*, 2730–2738. https://doi.org/10.3762/bjoc.21.210

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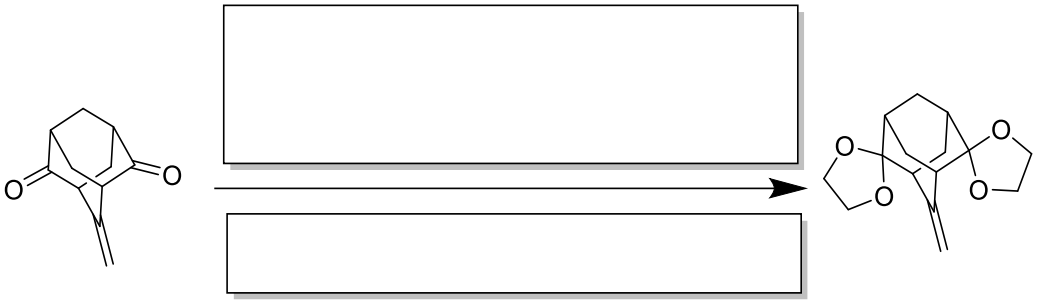

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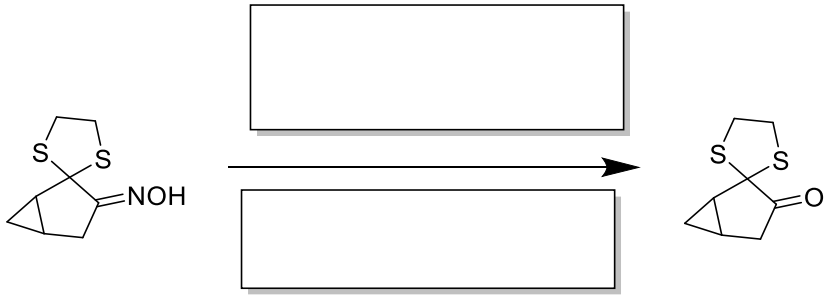

Kadunce, N.; St-Jean, O.; Cagulada, A.; Chang, W.-T. T.; Goldberg, A. F. G.; Huang, Z.; Kang, J.; Kim, J.; Kwon, K.; Lapina, O.; Lin, L.; Rainey, T. J.; Roever, L.; Shah, N. P.; Wolckenhauer, S. A. Synthetic Development and Scale-Up of a Complex Pyrazole Fragment of Lenacapavir. *Org. Process Res. Dev.* **2024**, *28* (8), 3368-3381. https://doi.org/10.1021/acs.oprd.4c00235

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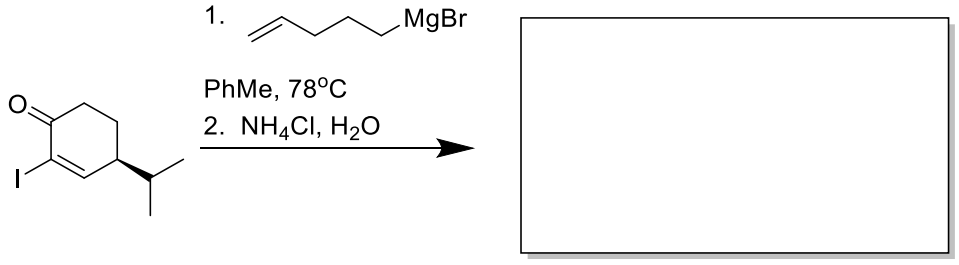

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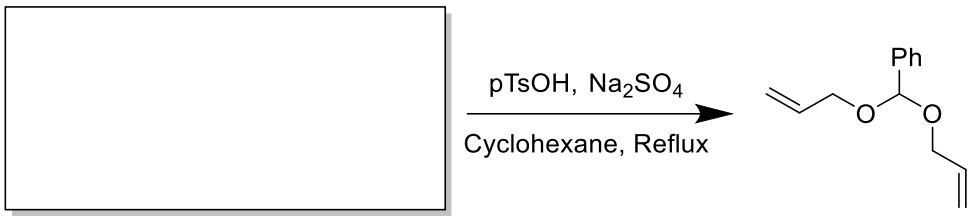

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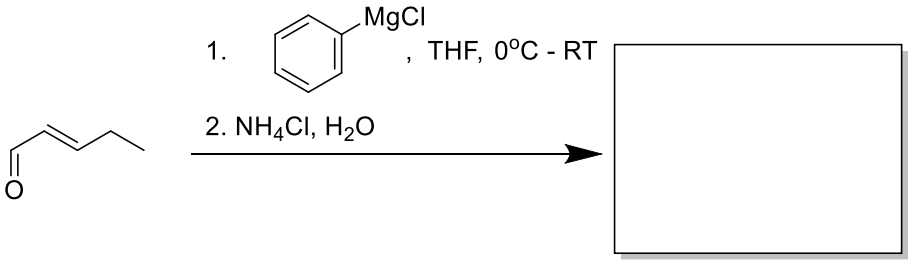
8a.1.13



Yang, X.; Zhao, D.; Liu, Y.; Zhu, C. Palladium-Catalyzed Migratory Allylic Sulfonylation of Allylic Alcohols Using Sulfonyl Hydrazides. *Org. Biomol. Chem.* **2026**, *24* (24), 5057–5063. https://doi.org/10.1039/D6OB00512H

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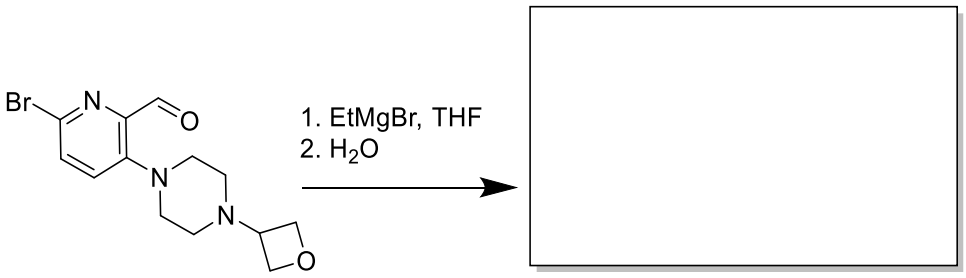

Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2026**, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

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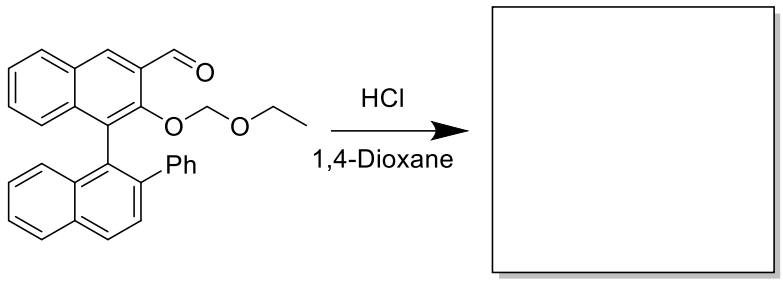

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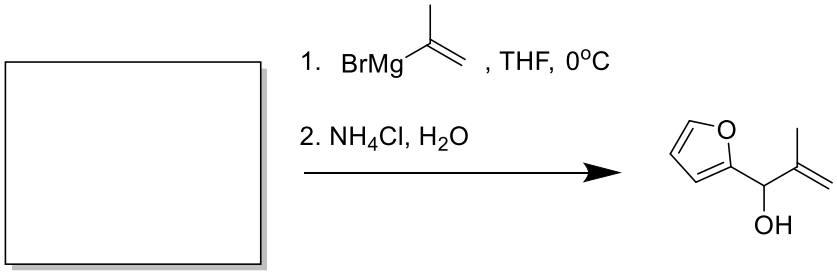

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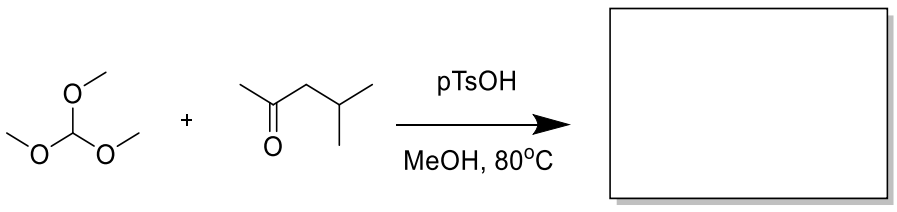
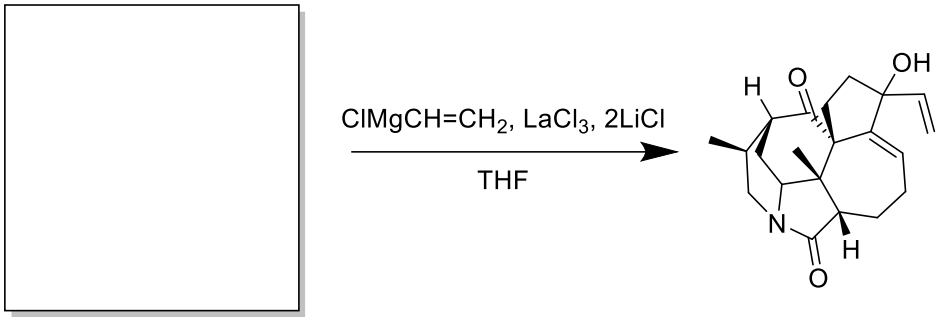


Wang, R.-H.; Li, J.-F.; Li, Y.; Qi, S.-L.; Zhang, T.; Luan, Y.-X.; Ye, M. Selective C(Sp^3)–H Cleavage of Enamides for Synthesis of 2-Pyridones via Ligand-Enabled Ni–Al Bimetallic Catalysis. *ACS Catal.* **2021**, *11* (2), 858–864. https://doi.org/10.1021/acscatal.0c04585

8a.1.18



Note: For an introductory organic chemistry course, you do not need to know how $LaCl_3$ and LiCl participate in the reaction.

Zhang, Y.; Chen, Y.; Xu, J. Total Synthesis of Daphniphyllum Alkaloids: (+)-Daphlongamine E, (+)-Calyciphylline R, and (–)-10-Deoxydaphnipaxianine A. *Synthesis* **2024**, *56* (08), 1273–1284. https://doi.org/10.1055/a-2244-1600

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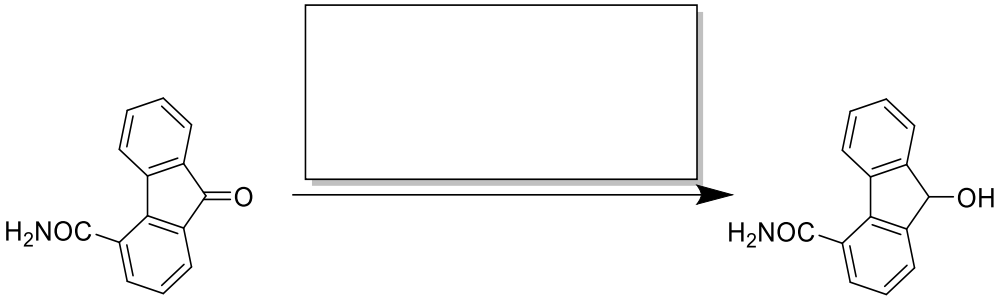

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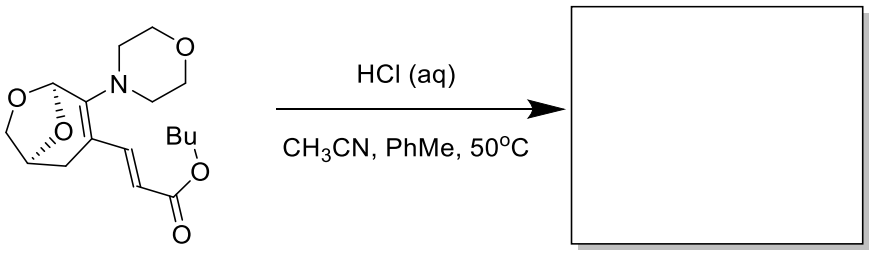

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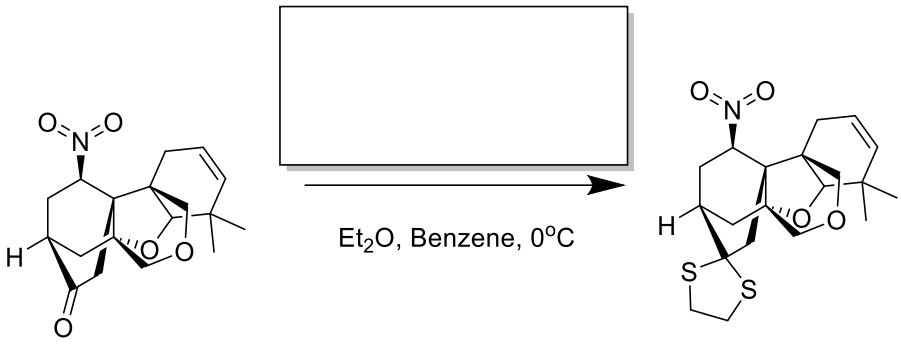

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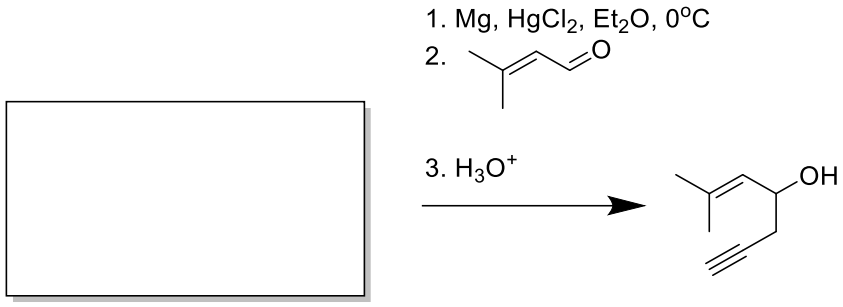

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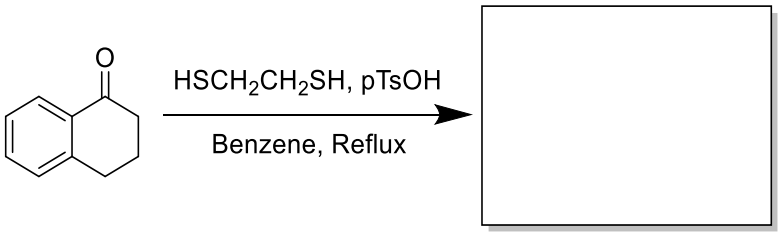

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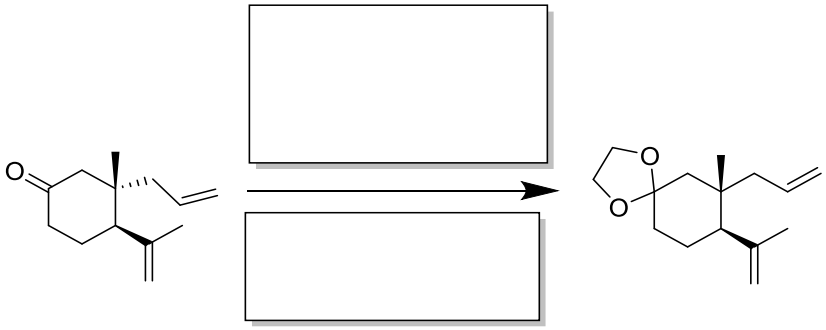

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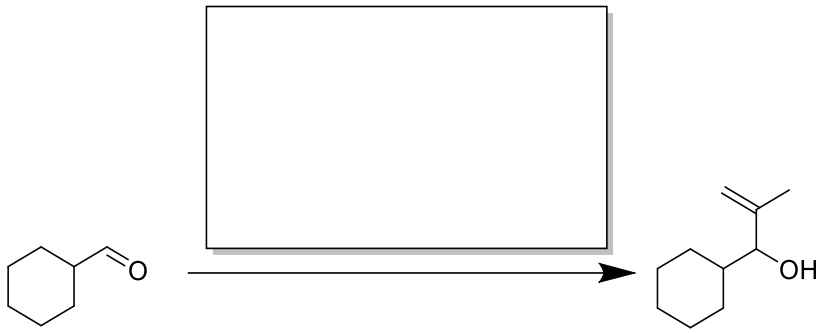

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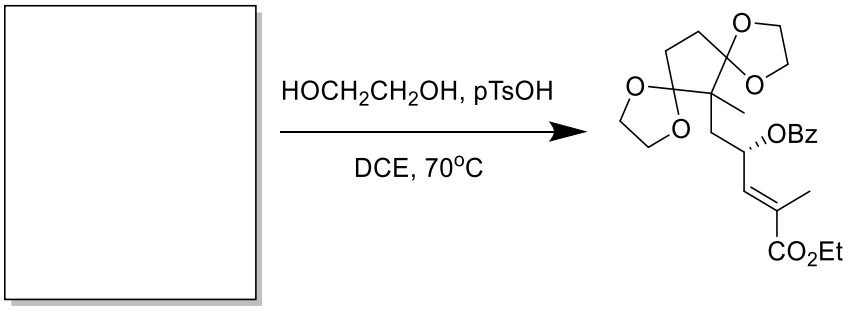
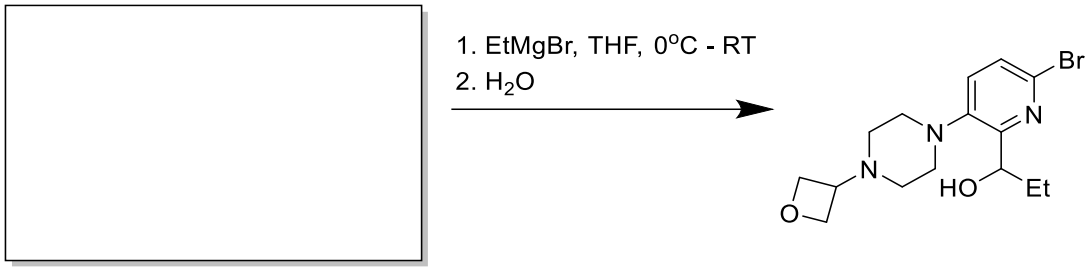
8a.1.26



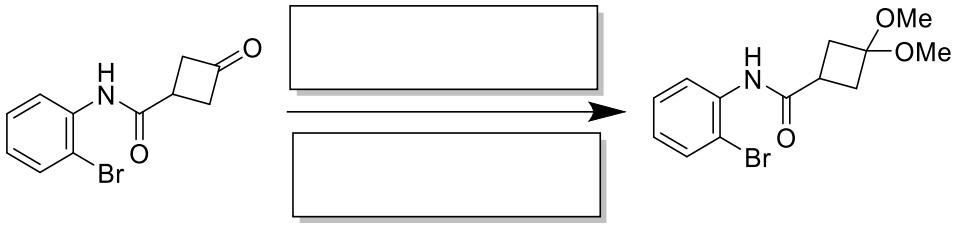
Ikeuchi, K.; Haraguchi, S.; Fujii, R.; Yamada, H.; Suzuki, T.; Tanino, K. Total Synthesis of (+)-Coriamyrtin via a Desymmetrizing Strategy Involving a 1,3-Cyclopentanedione Moiety. *Org. Lett.* **2023**, *25* (16), 2751–2755. https://doi.org/10.1021/acs.orglett.3c00249

8a.1.27



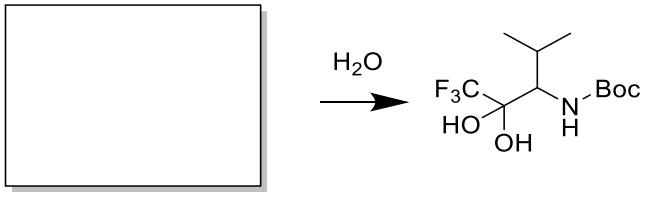
Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2026**, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

8a.1.28



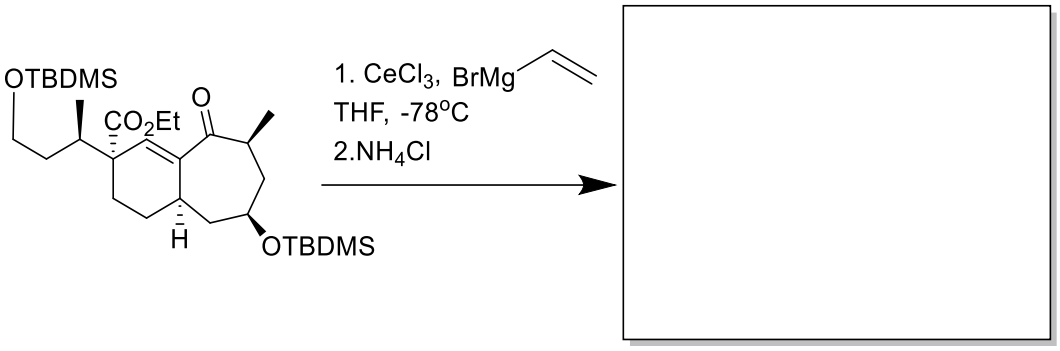
Cao, T. D. C.; Neufeld, K.; Zarate, C.; Nichols, C. J.; Lellek, V.; Deidda, R.; Conza, M.; Schleiss, P.; Rinderhagen, H.; Pye, P.; Muuronen, M.; Chen, W.; Tona, V.; Jouffroy, L.; Viereck, P.; Matcha, K. An Expedient Synthetic Route to the Long-Acting RSV Inhibitor JNJ-6231 via Stereoselective Enzymatic Amination and Regioselective Alkylation. *Org. Process Res. Dev.* **2026**, *30* (1), 121–134. https://doi.org/10.1021/acs.oprd.5c00352

8a.1.29



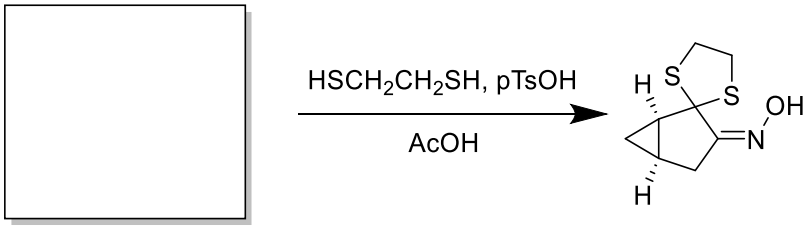
Paszek, K.; Siodła, T.; Janicki, M.; Ludwików, A.; Koroniak, H.; Koroniak-Szejn, K. Toward Novel Trifluoromethylated Peptidomimetics: A Case Study of Cathepsin C Inhibitors. *Eur. J. Org. Chem.* **2026**, *29* (1), e202500773. https://doi.org/10.1002/ejoc.202500773

8a.1.30



Mao, H.-K.; Wang, Q.; Xu, J. Enantioselective Total Synthesis of Fortalpinoid Q via a TEMPO^{+} BF_4^{-} -Mediated Dehydrative Nazarov Cyclization. *J. Am. Chem. Soc.* **2025**, *147* (11), 9079–9084. https://doi.org/10.1021/jacs.5c00319

8a.1.31



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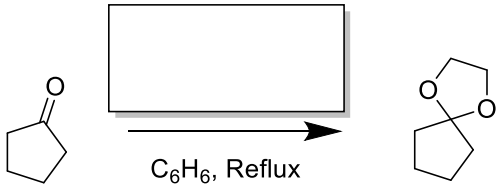
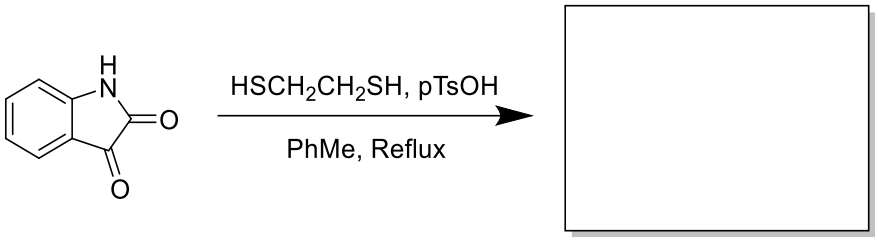
8a.1.32



Note: The authors did not have to use an acid catalyst for this reaction to work.

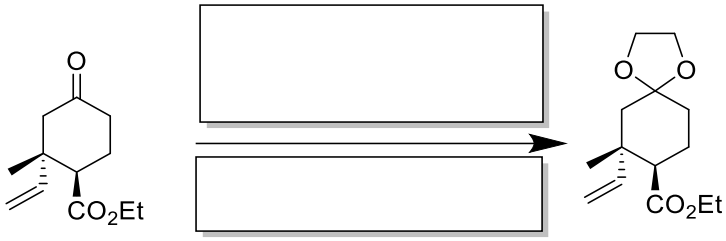
Bartonek, A.; Klapötke, T. M.; Krumm, B. Sensitive 1,4-Disubstituted Nitro-Containing Cubanes: Structures and Properties. *J. Org. Chem.* **2023**, *88* (18), 12884-12890. https://doi.org/10.1021/acs.joc.3c00384

8a.1.33



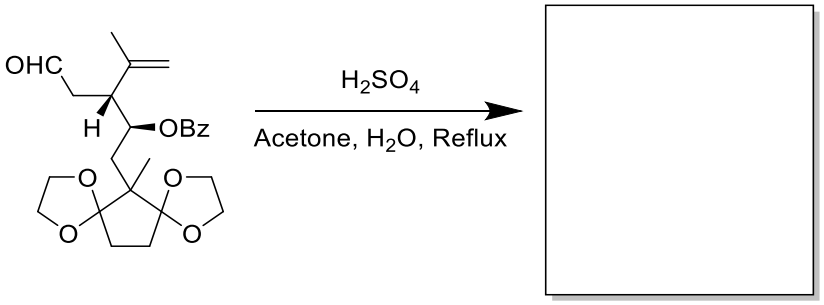
Lamba, M.; Kumar, M.; Mane, M. V.; Goswami, A. Selectfluor-Mediated Directing Group and Transition Metal Catalyst-Free Site-Selective C7 Fluorination of 2-Oxindoles. *Adv. Synth. Catal.* **2026**, *368* (12), e70538. https://doi.org/10.1002/adsc.70538

8a.1.34



Yue, G.; Yang, L.; Yuan, C.; Du, B.; Liu, B. Total Syntheses of Lindenane-Type Sesquiterpenoids: (±)-Chloranthalactones A, B, F, (±)-9-Hydroxy Heterogorgiolide, and (±)-Shizukanolide E. *Tetrahedron* **2012**, *68* (47), 9624–9637. https://doi.org/10.1016/j.tet.2012.09.053

8a.1.35

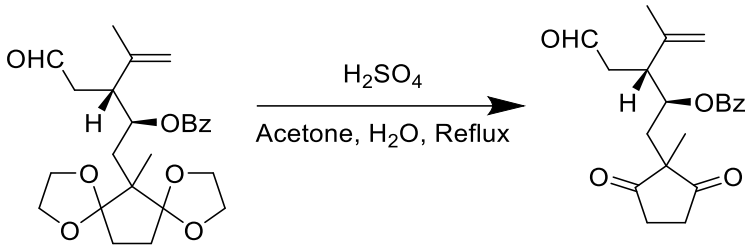


Ikeuchi, K.; Haraguchi, S.; Fujii, R.; Yamada, H.; Suzuki, T.; Tanino, K. Total Synthesis of (+)-Coriamyrtin via a Desymmetrizing Strategy Involving a 1,3-Cyclopentanedione Moiety. *Org. Lett.* **2023**, *25* (16), 2751–2755. https://doi.org/10.1021/acs.orglett.3c00249

Section 8a – Mechanism Questions

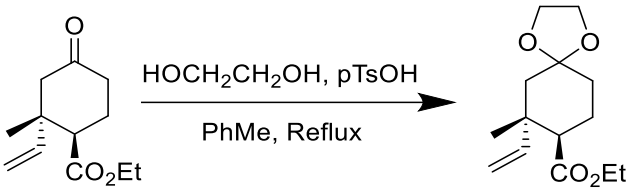
Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

8a.2.1



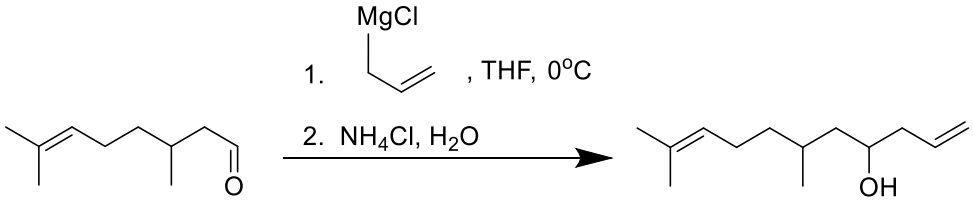
Ikeuchi, K.; Haraguchi, S.; Fujii, R.; Yamada, H.; Suzuki, T.; Tanino, K. Total Synthesis of (+)-Coriamyrtin via a Desymmetrizing Strategy Involving a 1,3-Cyclopentanedione Moiety. *Org. Lett.* **2023**, *25* (16), 2751–2755. https://doi.org/10.1021/acs.orglett.3c00249

8a.2.2



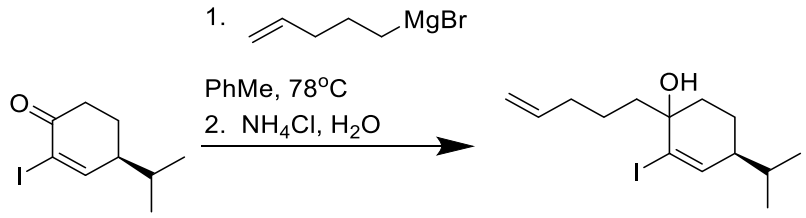
Yue, G.; Yang, L.; Yuan, C.; Du, B.; Liu, B. Total Syntheses of Lindenane-Type Sesquiterpenoids: (±)-Chloranthalactones A, B, F, (±)-9-Hydroxy Heterogorgiolide, and (±)-Shizukanolide E. *Tetrahedron* **2012**, *68* (47), 9624–9637. https://doi.org/10.1016/j.tet.2012.09.053

8a.2.3



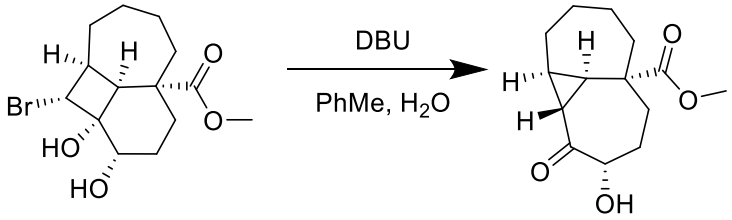
Zhang, Z.-K.; Lu, J.-A.; Zhang, S.; Zhang, J.-X.; Wang, D.-M.; Wu, Y.; Xu, Y.-Q.; Cao, Z.-Y.; Wang, P. Nickel-Catalyzed Remote Substitution of Alcohols. *J. Am. Chem. Soc*. **2026**, *148* (20), 20356–20363. https://doi.org/10.1021/jacs.6c07181

8a.2.4



Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* **2009**, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

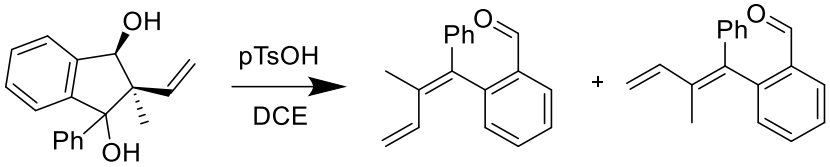
8a.2.5



Note: DBU is a base, you can represent it as "R_3N" in your reaction mechanism.

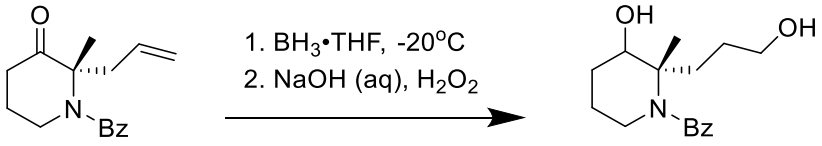
Cao, S.-Y.; Yue, H.-J.; Zhu, M.-Q.; Xu, L. Synthesis of Tricyclo[7.2.1.$0^{9,10}$]Dodecan-11-One Core Ring Systems of Norditerpenoid Alkaloids and Racemulosine. *Org. Chem. Front.* **2020**, *7* (7), 933–937. https://doi.org/10.1039/D0QO00088D

8a.2.6



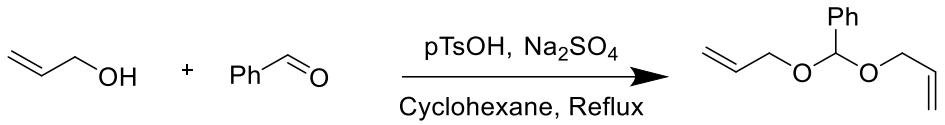
Mondal, A.; Satpathi, B.; Ramasastry, S. S. V. Phosphine-Catalyzed Intramolecular Vinylogous Aldol Reaction of α-Substituted Enones. *Org. Lett*. **2022**, *24* (1), 256–261. https://doi.org/10.1021/acs.orglett.1c03913.

8a.2.7



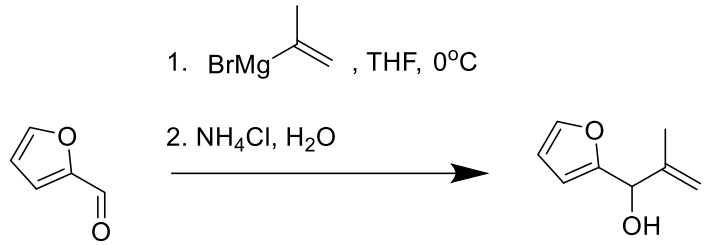
Wang, Z.; Chen, D.; Chang, J.; Li, Y.; Su, Y.; Tang, P.; Chen, F.-E. Enantioselective Synthesis of Functionalized 2,2-Disubstituted Piperidines Enabled by Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation. *Org. Lett.* **2026**, *28* (2), 794–799. https://doi.org/10.1021/acs.orglett.5c04932

8a.2.8



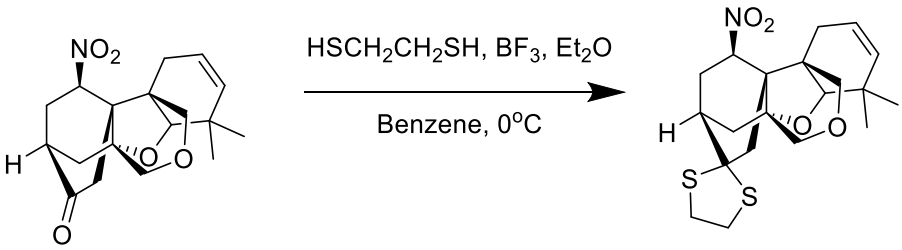
Ghosh, A. K.; Belcher, M. R. Lewis Acid-Catalyzed Vinyl Acetal Rearrangement of 4,5-Dihydro-1,3-Dioxepines: Stereoselective Synthesis of *Cis*- and *Trans*- 2,3-Disubstituted Tetrahydrofurans. *J. Org. Chem.* **2020**, *85* (16), 10399–10412. https://doi.org/10.1021/acs.joc.0c00390

8a.2.9



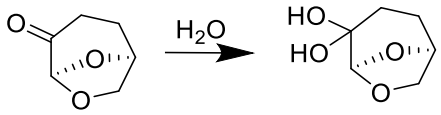
Petrone, D. A.; Malik, H. A.; Clemenceau, A.; Lautens, M. Functionalized Chromans and Isochromans via a Diastereoselective Pd(0)-Catalyzed Carboiodination. *Org. Lett*. **2012**, *14* (18), 4806–4809. https://doi.org/10.1021/ol302111y

8a.2.10



Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. Enantioselective Total Synthesis of (−)-Maoecrystal V. *J. Am. Chem. Soc.* **2014**, *136* (51), 17750–17756. https://doi.org/10.1021/ja5109694

8a.2.11



Dejaegere, A.; Napoli, A.; Heugebaert, T. S. A.; Stevens, C. V. Continuous Dihydrolevoglucosenone Recovery Using Commercial Membrane Technology. *Org. Process Res. Dev.* **2025**, *29* (4), 1076–1082. https://doi.org/10.1021/acs.oprd.4c00494

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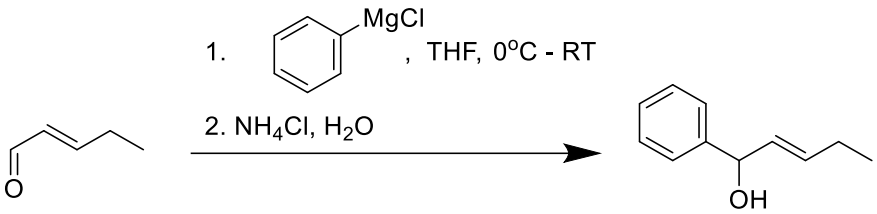

Yang, X.; Zhao, D.; Liu, Y.; Zhu, C. Palladium-Catalyzed Migratory Allylic Sulfonylation of Allylic Alcohols Using Sulfonyl Hydrazides. *Org. Biomol. Chem.* **2026**, *24* (24), 5057–5063. https://doi.org/10.1039/D6OB00512H

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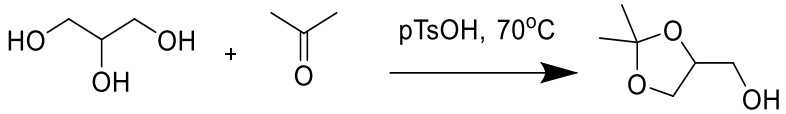

Chang, J. J.; Kumar, M.; Kashatus, R. C.; Tomaselli, D. J.; Kim, D. K. Substitutive Approach Toward Heteroaromatic Amino Alcohols Accessed Through Dioxolanyl Radical Linchpin. *Adv. Synth. Catal.* **2026**, *368* (7), e70405. https://doi.org/10.1002/adsc.70405

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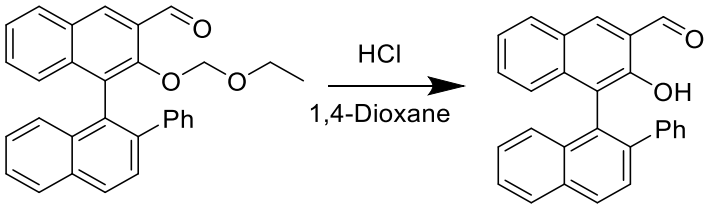

Sandvoß, A.; Maag, H.; Daniliuc, C. G.; Schollmeyer, D.; Wahl, J. M. Dynamic Kinetic Resolution of Transient Hemiketals: A Strategy for the Desymmetrisation of Prochiral Oxetanols. *Chem. Sci.* **2022**, *13* (21), 6297–6302. https://doi.org/10.1039/D2SC01547A

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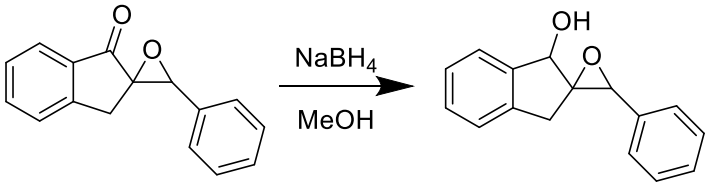
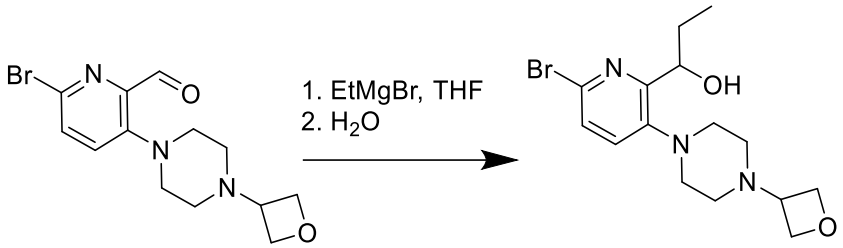


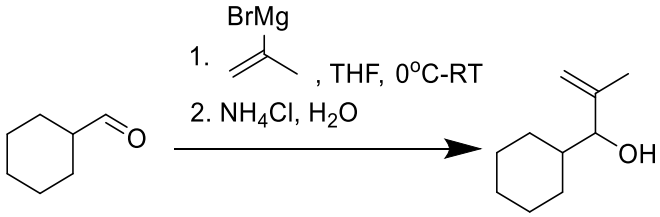
Qin, L.; Li, M.; Wang, X.; You, C.; Deng, G.; Chen, Y. Engineering of $P450_{PL2}$ Monooxygenase for the Stereoselective Synthesis of (*R*)-Styrene Oxides. *Org. Lett.* **2026**, *28* (8), 2567–2572. https://doi.org/10.1021/acs.orglett.5c05206

8a.2.16



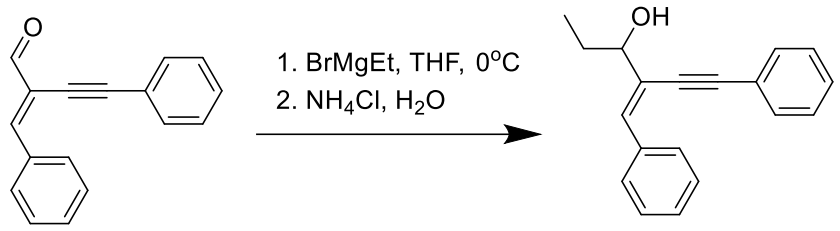
Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2026**, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

8a.2.17



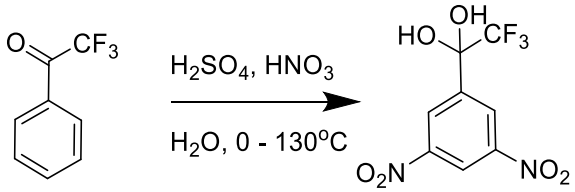
Han, Y.-F.; Hua, K.; Zhao, X.; Li, J.-H. Stereoselective Synthesis of (*E*)-Allylic Sulfones by Photocatalytic Desilyloxylative Sulfonylation of Allyl Silyl Ethers with Thiosulfonates. *Org. Lett.* **2026**, *28* (18), 5698–5703. https://doi.org/10.1021/acs.orglett.6c01026

8a.2.18



Huang, M.; Tang, Y.; Jin, J.; Cui, Z.; Zhou, L.; Zheng, B.; Guo, H. Synthesis of Stilbene Derivatives via Phosphine-Catalyzed Cascade [2+4] Annulation/Decarboxylative Aromatization of Yne-Enones with α-Pyrones. *Org. Lett*. **2026**, *28* (8), 2813–2817. https://doi.org/10.1021/acs.orglett.6c00564

8a.2.19



Sandvoß, A.; Maag, H.; Daniliuc, C. G.; Schollmeyer, D.; Wahl, J. M. Dynamic Kinetic Resolution of Transient Hemiketals: A Strategy for the Desymmetrisation of Prochiral Oxetanols. *Chem. Sci.* **2022**, *13* (21), 6297–6302. https://doi.org/10.1039/D2SC01547A

Section 8b: Aldehydes and Ketones 2

Required foundation for this section:

Nucleophilic addition

Imine and enamine formation

Cyanohydrin formation

Wittig reaction

Bayer-Villiger oxidation

Metal reduction of aldehyde and ketone

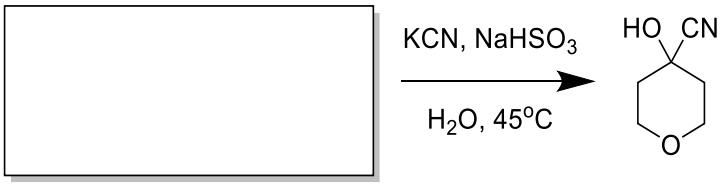
Wolff-Kishner reduction

Aldehyde oxidation

Section 8b – Box-Type Questions

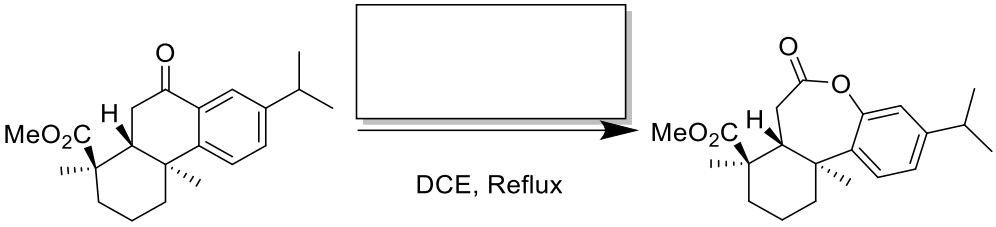
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

8b.1.1



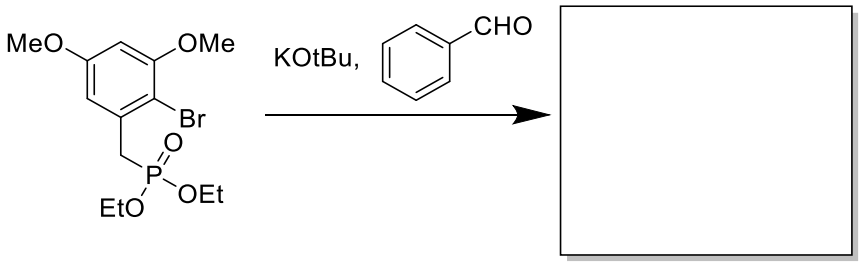
Holovko-Kamoshenkova, O.; Tošner, Z.; Císařová, I.; Hrdina, R. C–H Amination of Enolizable and Nonenolizable Ketones. *Org. Biomol. Chem.* **2025**, *23* (12), 2818–2822. https://doi.org/10.1039/D5OB00009B

8b.1.2



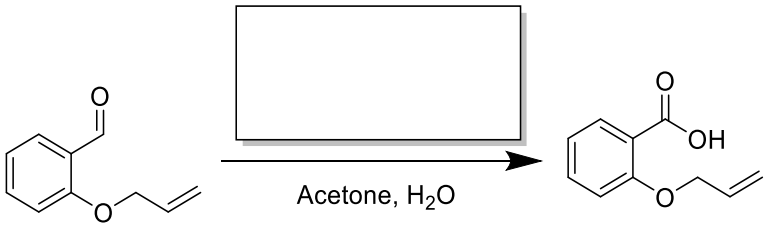
Ikonnikova, V. A.; Solyev, P. N.; Al Mufti, A. M.; Kungurtsev, K. D.; Korlyukov, A. A.; Baranov, M. S.; Mikhaylov, A. A. Synthesis of Chroman Derivatives by Group Transposition and Atom Swapping in 1-Tetralones: Single-Atom Editing Enabled by Oxidative Ring Contraction of Benzoxepine Silyl Ketene Acetals. *Angew. Chem. Int. Ed.* **2025**, *64* (31), e202506564. https://doi.org/10.1002/anie.202506564

8b.1.3



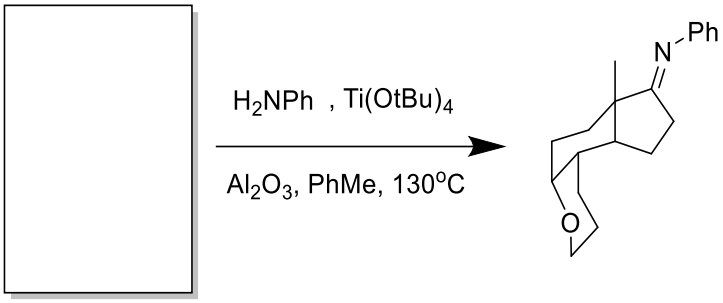
Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. Total Synthesis of Diverse Carbogenic Complexity within the Resveratrol Class from a Common Building Block. *J. Am. Chem. Soc.* **2009**, *131* (5), 1753–1765. https://doi.org/10.1021/ja806183r

8b.1.4



Cheng, Y. A.; Chen, T.; Tan, C. K.; Heng, J. J.; Yeung, Y.-Y. Efficient Medium Ring Size Bromolactonization Using a Sulfur-Based Zwitterionic Organocatalyst. *J. Am. Chem. Soc.* **2012**, *134* (40), 16492-16495. https://doi.org/10.1021/ja307210n

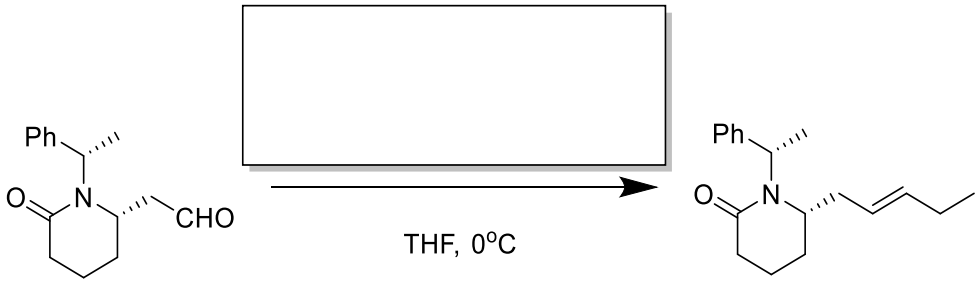
8b.1.5



Hint: Ti(Ot-Bu)$_4$ is used to supply a Lewis acid.

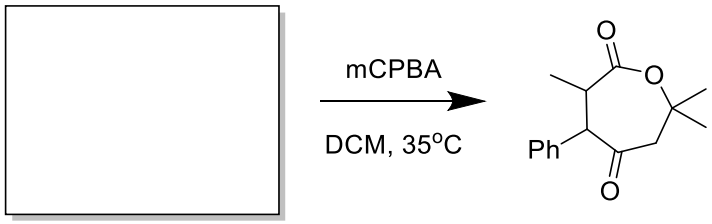
Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W. Photocatalyzed Epimerization of Quaternary Stereocenters. *J. Am. Chem. Soc.* **2025**, *147* (13), 11080-11088. https://doi.org/10.1021/jacs.4c16769

8b.1.6



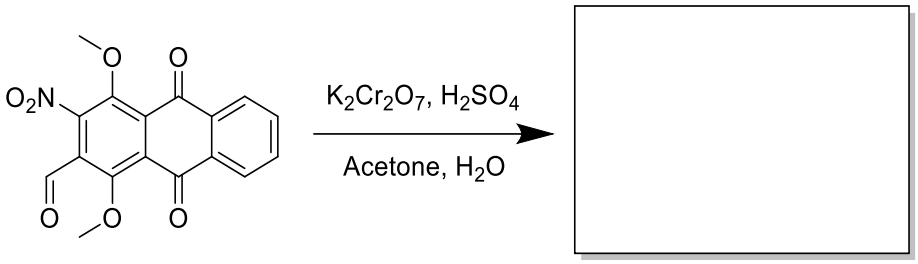
Nishikawa, K.; Ono, Y.; Mori, S.; Takayama, K.; Ihara, M.; Matsuda, K.; Morimoto, Y. Divergent Nine-Step Syntheses of Perhydrohistrionicotoxin Analogs and Their Inhibition Activity Toward Chicken A4β2-Neuronal Nicotinic Acetylcholine Receptors. *J. Org. Chem.* **2024**, *89* (6), 4128–4133. https://doi.org/10.1021/acs.joc.3c02988

8b.1.7



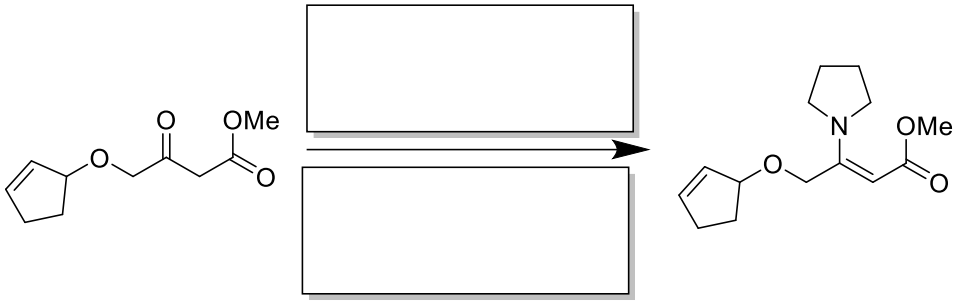
Xiong, J.; Wang, Y.; Tang, X. Binaphthalene-Modified *C* -Scorpionate Zinc Catalysts for Ring-Opening Polymerization of Bio-Based *γ* -Ketolactones to High-Molar-Mass Degradable Polyesters. *Angew. Chem. Int. Ed.* **2026**, *65* (3), e17535. https://doi.org/10.1002/anie.202517535

8b.1.8



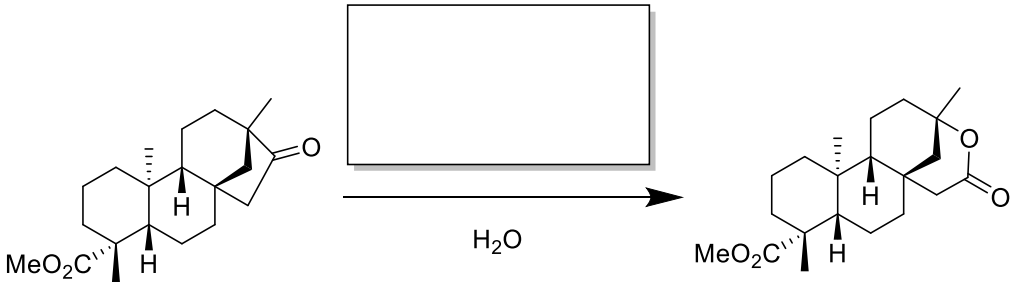
Litvinova, V. A.; Gostev, A. S.; Tikhomirov, A. S.; Shchekotikhin, A. E. New Heteroarene-Fused Anthraquinones: Synthesis and PyBOP-Mediated Amination. *Tetrahedron* **2023**, *149*, 133722. https://doi.org/10.1016/j.tet.2023.133722

8b.1.9



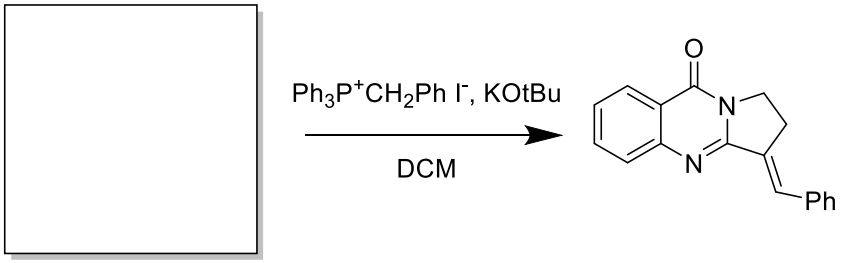
Ho, G.-M.; Tseng, C.-W.; Liu, Y.-H.; Li, Y.-J. Direct Synthesis of 5-Cycloalkene-Substituted γ-Butenolides via [2,3]-Wittig Rearrangement of Vinylogous Urethanes. *Synth. Commun.* **2026**, *56* (4), 318-327. https://doi.org/10.1080/00397911.2026.2621827

8b.1.10



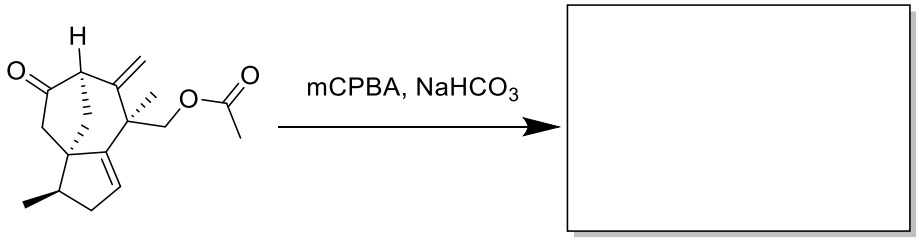
Holth, T. A. D.; Walters, M. A.; Hutt, O. E.; Georg, G. I. Diversity-Oriented Library Synthesis from Steviol and Isosteviol-Derived Scaffolds. *ACS Comb. Sci.* **2020**, *22* (3), 150–155. https://doi.org/10.1021/acscombsci.9b00186

8b.1.11



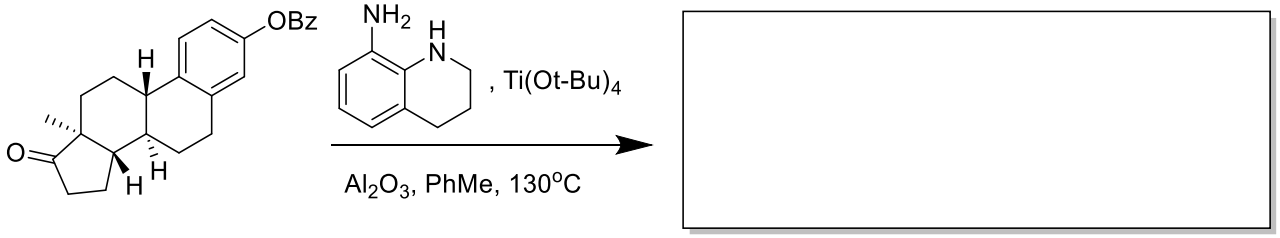
D'Almeida, R. E.; Chen, P.; Huang, Y.; Goetz, E.; Sammeta, V. R.; Yang, B.; Rao, R. P.; Rasapalli, S.; Elfawal, M. A. Design, Synthesis, and Biological Evaluation of a Focused Pyrrolo- and Pyrido-Quinazolinone Natural Products-Templated Library for Anti-Fungal and Anthelmintic Activities. *Bioorg. Med. Chem.* **2026**, *134*, 118517. https://doi.org/10.1016/j.bmc.2025.118517

8b.1.12



Fu, P.; Liu, T.; Shen, Y.; Lei, X.; Xiao, T.; Chen, P.; Qiu, D.; Wang, Z.; Zhang, Y. Divergent Total Syntheses of Illicium Sesquiterpenes through Late-Stage Skeletal Reorganization. *J. Am. Chem. Soc.* **2023**, *145* (33), 18642-18648. https://doi.org/10.1021/jacs.3c06442

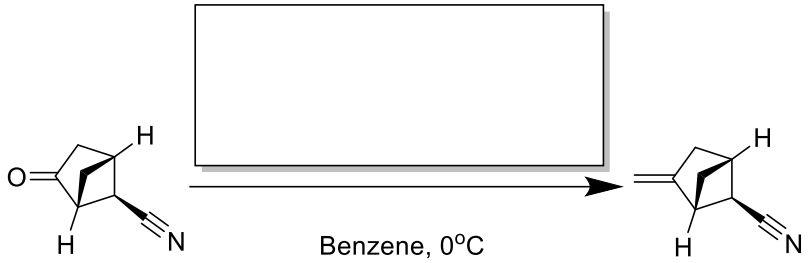
8b.1.13



Hint: $Ti(Ot\text{-}Bu)_4$ is a Lewis acid.

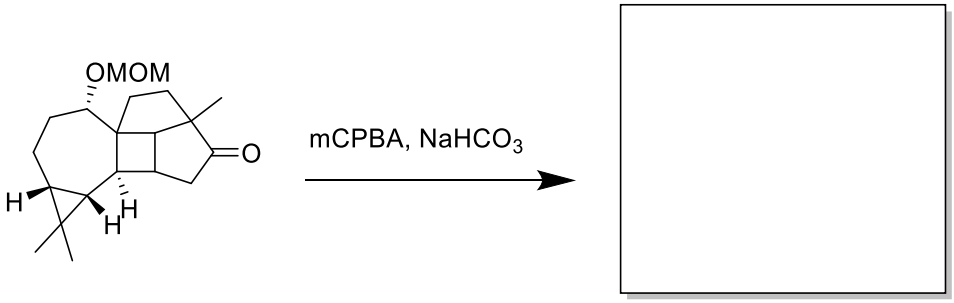
Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W. Photocatalyzed Epimerization of Quaternary Stereocenters. *J. Am. Chem. Soc.* **2025**, *147* (13), 11080-11088. https://doi.org/10.1021/jacs.4c16769

8b.1.14



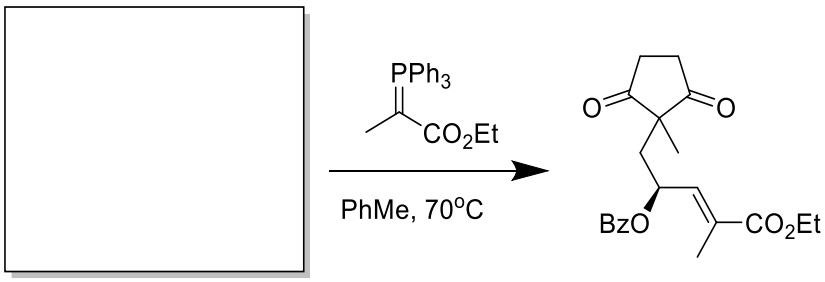
Mehta, G.; Singh, S. R.; Balanarayan, P.; Gadre, S. R. Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]Hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects. *Org. Lett.* **2002**, *4* (14), 2297–2300. https://doi.org/10.1021/ol026005d

8b.1.15



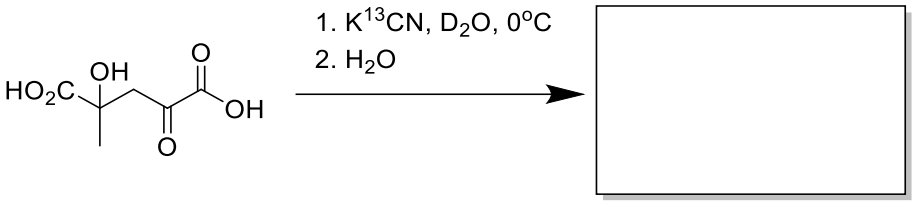
Liu, M.; Wu, C.; Xie, X.; Li, H.; She, X. Total Synthesis of the Euphorbia Diterpenoid Pepluacetal. *Angew. Chem. Int. Ed.* **2024**, *63* (21), e202400943. https://doi.org/10.1002/anie.202400943

8b.1.16



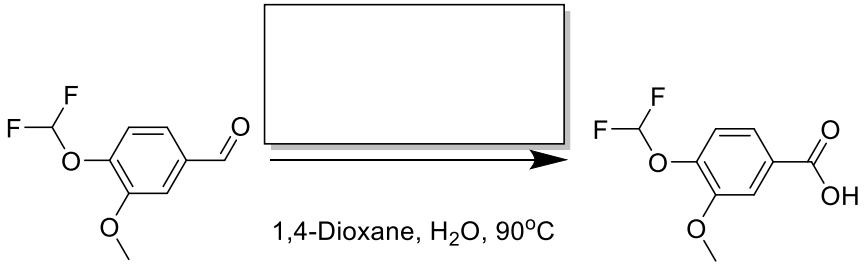
Kuwabara, M.; Matsuo, A.; Kamo, S.; Matsuzawa, A.; Sugita, K. Stereoselective Convergent Synthesis of Carbon Skeleton of Cotylenin A Aglycone. *Synthesis* **2021**, *53* (12), 2092–2102. https://doi.org/10.1055/s-0040-1706684

8b.1.17



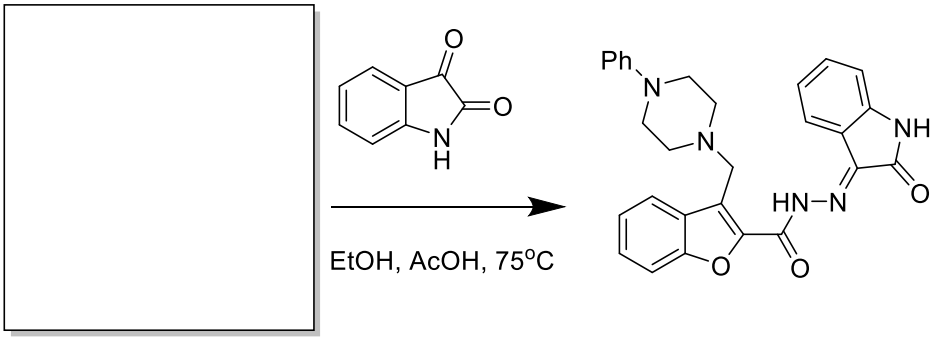
Sharma, S.; Yang, Y.; Lee, J.-W. A Prebiotic Route to Lactate from Acetaldehyde, Cyanide and Carbon Dioxide. *Chem. Eur. J.* **2025**, *31* (11), e202403763. https://doi.org/10.1002/chem.202403763

8b.1.18



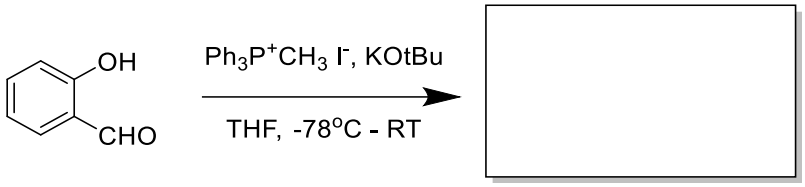
Mungalpara, M. N.; Wu, X.; Ma, X.; Zhu, Z.; Jiang, M.; Pike, V. W.; Lu, S.; Zhang, H.; Wu, Z.; Kinon, P. O.; Huang, Y.; Nicewicz, D. A.; Li, Z. Deoxyradiofluorination of Phenols via a Difluoromethoxy Nucleofuge Enabled by Organic Photoredox Catalysis. *ACS Cent. Sci.* **2026**, *12* (5), 638–648. https://doi.org/10.1021/acscentsci.6c00127

8b.1.19



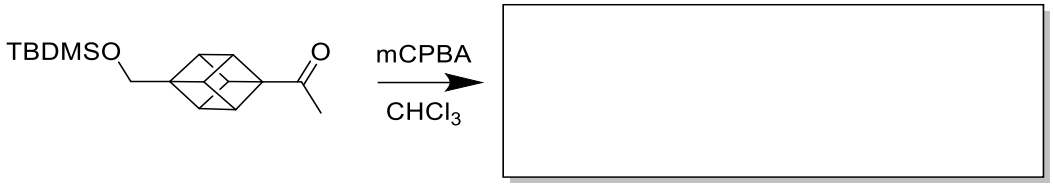
Eldehna, W. M.; Tawfik, H. O.; Nafie, M. S.; Al Kamaly, O.; El-Hamaky, A. A.; El Hassab, M. A.; Elsayed, Z. M.; Elnaggar, Y. S. R.; Al-Karmalawy, A. A.; Di Giacomo, V.; Balaha, M. Novel Benzofuran-Conjugated Indolin-2-ones as Anticancer Agents: Design, Synthesis, Biological Assessments, and Molecular Modeling Insights. *Bioorg. Chem.* **2025**, *160*, 108494. https://doi.org/10.1016/j.bioorg.2025.108494

8b.1.20



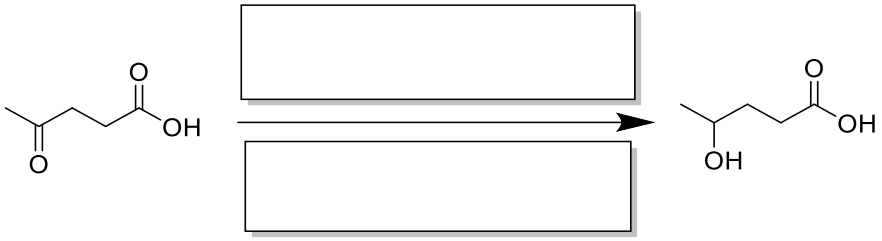
Parasram, M.; Iaroshenko, V. O.; Gevorgyan, V. Endo-Selective Pd-Catalyzed Silyl Methyl Heck Reaction. *J. Am. Chem. Soc.* **2014**, *136* (52), 17926-17929. https://doi.org/10.1021/ja5104525

8b.1.21



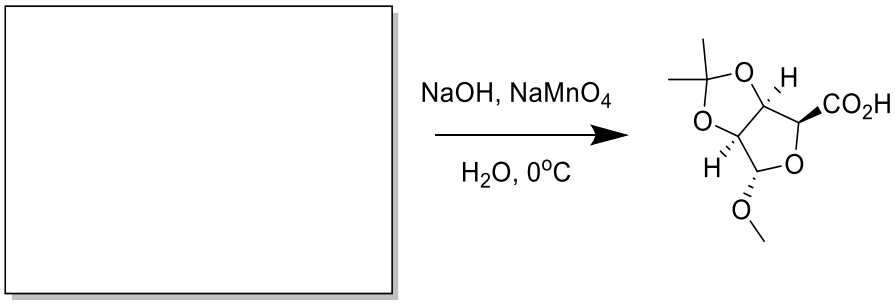
Hind, J.; Fallis, I. A.; Platts, J. A.; Tredwell, M. The Baeyer-Villiger Oxidation of Cubyl Ketones: A Synthetic Route to Functionalized Cubanols. *Org. Lett.* **2025**, *27* (33), 9218-9222. https://doi.org/10.1021/acs.orglett.5c02760

8b.1.22



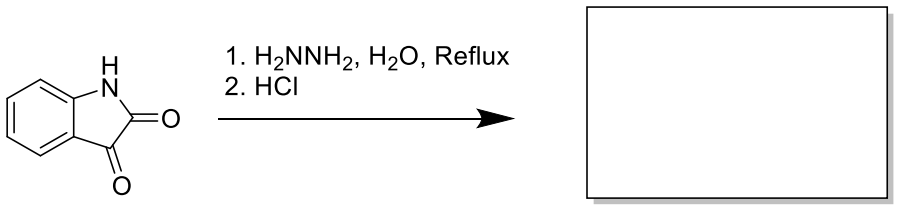
Sepulveda Lanziano, C. A.; Rodella, C. B.; Guirardello, R. Evaluation of Kinetic Models for the Catalytic Hydrogenation of Levulinic Acid to γ-Valerolactone over Nickel Catalyst Supported by Titania. *Molecules* **2025**, *30* (7), 1400. https://doi.org/10.3390/molecules30071400

8b.1.23



Sedaghat, S. Synthesis of Cholesteryl-(3,4-dihydroxy-5-methoxy tetrahydro-furan-2-yl) Methanone. *Afr. J. Pure Appl. Chem.* **2013**, *7* (1), 31-34. https://doi.org/10.5897/AJPAC11.007

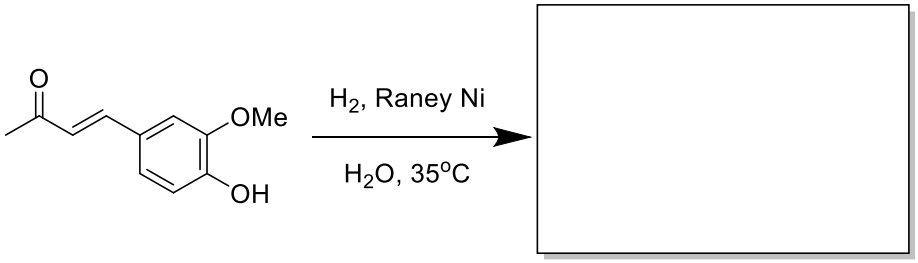
8b.1.24



Note: Although the conditions in step 2 are acidic and you would typically learn that this reaction occurs under basic conditions, please assume they lead to the same product.

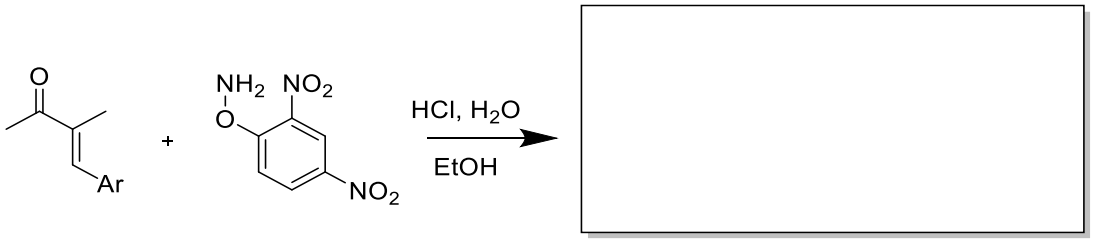
Yousefian, M.; Hashemi, M.; Eskandarpour, V.; Zarghi, A.; Hadizadeh, F.; Ghodsi, R. New Indolin-2-ones, Possessing Sunitinib Scaffold as HDAC Inhibitors and Anti-Cancer Agents with Potential VEGFR Inhibition Activity: Design, Synthesis and Biological Evaluation. *Bioorg. Chem.* **2025**, *156*, 108231. https://doi.org/10.1016/j.bioorg.2025.108231

8b.1.25



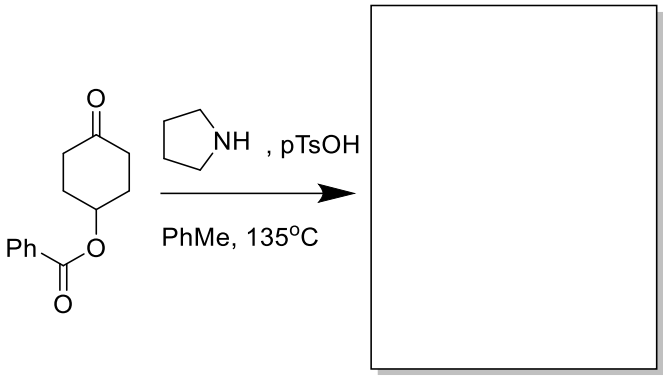
Zhang, Y.; Fayad, E.; Katouah, H. A.; Qin, H.-L. Solvent-Controlled and Highly Chemoselective Reduction of α,β-Unsaturated Ketones and Aldehydes. *J. Org. Chem.* **2025**, *90* (16), 5704–5709. https://doi.org/10.1021/acs.joc.5c00151

8b.1.26



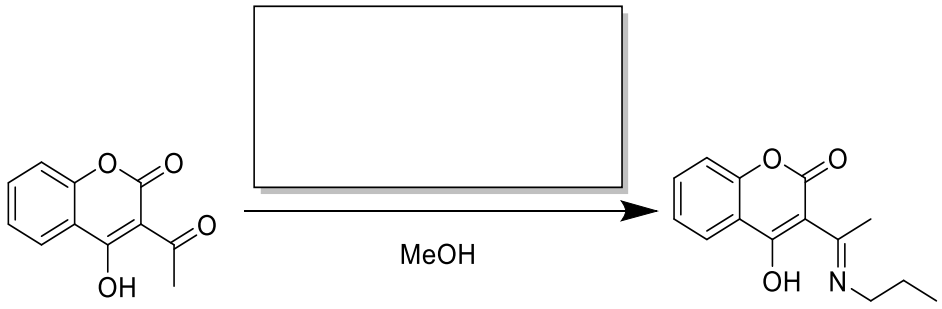
Zeng, Q.-Y.; Zhang, Y.-Q.; Cheng, X.-Y.; Xu, H.; Dai, H.-X. Synthesis of Polysubstituted Pyrroles via (2 + 2 + 1) Cyclization of Enone Oxime Ethers with Alkynes and Diaziridinone. *J. Org. Chem.* **2026**, *91* (3), 1271–1275. https://doi.org/10.1021/acs.joc.5c01879

8b.1.27



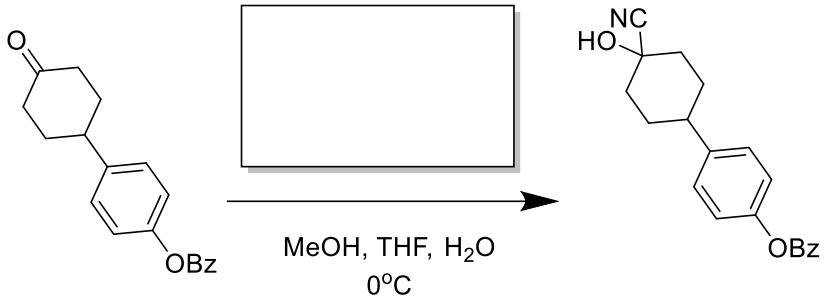
Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in Sp^3 -Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536–542. https://doi.org/10.1126/science.aef0610

8b.1.28



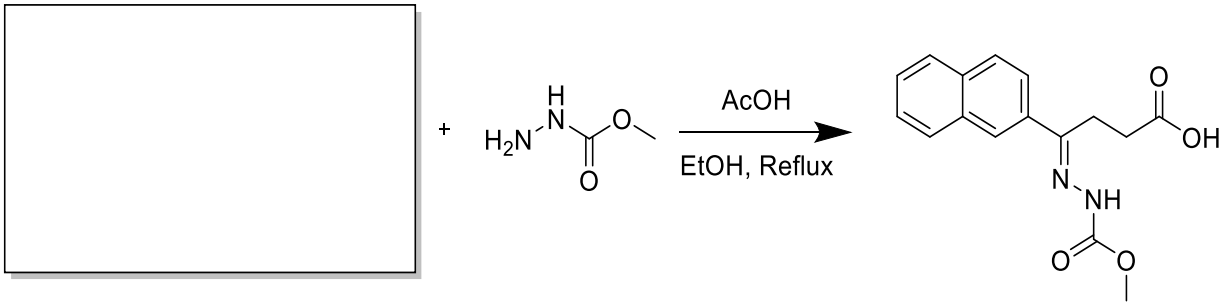
Aarjane, M.; Slassi, S.; Ait Mouha, M.; El-Ghayoury, A.; Yamni, K.; Amine, A. A New Coumarin Derivative: Synthesis, Crystal Structure, Computational Studies, and Dual Antioxidant–Antibacterial Activity. *J. Mol. Struct.* **2026**, *1349*, 143839. https://doi.org/10.1016/j.molstruc.2025.143839

8b.1.29



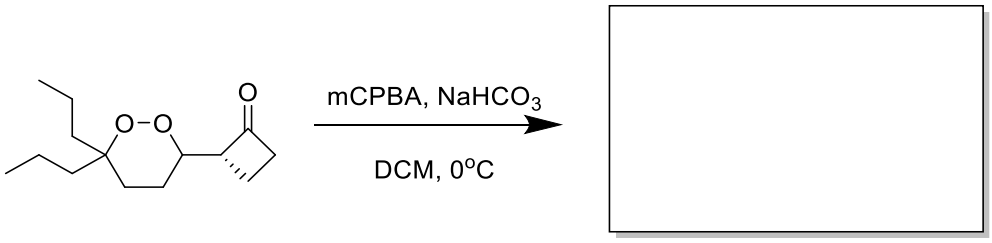
Amatya, E.; Subramanian, C.; Long, R.; McNamara, K.; Cohen, M. S.; Blagg, B. S. J. The Investigation of Hsp90C-Terminal Inhibitors Containing Amide Bioisosteres. *ChemMedChem* **2024**, *19* (24), e202400418. https://doi.org/10.1002/cmdc.202400418

8b.1.30



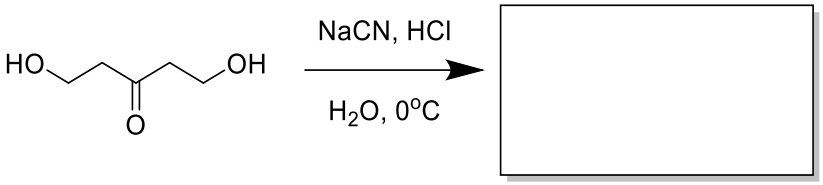
Cranwell, P. B.; Russell, A.; Smith, C. Methyl Hydrazinocarboxylate as a Practical Alternative to Hydrazine in the Wolff-Kishner Reaction. *Synlett* **2016**, *27* (1), 131-135. https://doi.org/10.1055/s-0035-1560805

8b.1.31



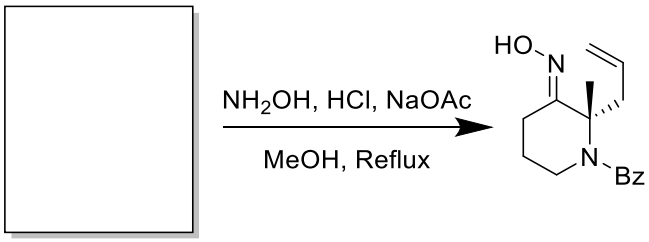
Champciaux, B.; Jamey, N.; Figadère, B.; Ferrié, L. Peroxycarbenium-Mediated Asymmetric Synthesis of 1,2-Dioxanes and 1,2-Dioxolanes. *J. Am. Chem. Soc.* **2025**, *147* (4), 3353–3359. https://doi.org/10.1021/jacs.4c13899

8b.1.32



Yerabolu, J. R.; Liotta, C. L.; Krishnamurthy, R. Anchimeric-Assisted Spontaneous Hydrolysis of Cyanohydrins Under Ambient Conditions: Implications for Cyanide-Initiated Selective Transformations. *Chem. Eur. J.* **2017**, *23* (36), 8756–8765. https://doi.org/10.1002/chem.201701497

8b.1.33

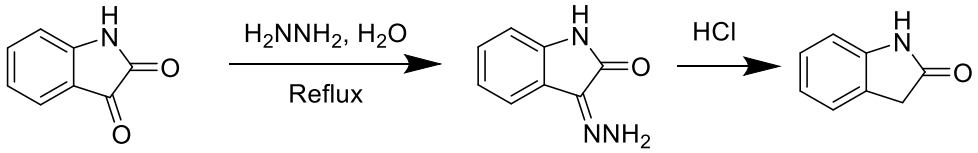


Wang, Z.; Chen, D.; Chang, J.; Li, Y.; Su, Y.; Tang, P.; Chen, F.-E. Enantioselective Synthesis of Functionalized 2,2-Disubstituted Piperidines Enabled by Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation. *Org. Lett.* **2026**, *28* (2), 794–799. https://doi.org/10.1021/acs.orglett.5c04932

Section 8b – Mechanism Questions

Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

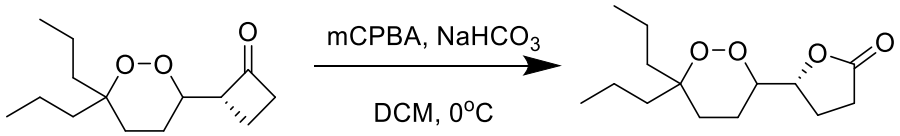
8b.2.1



Note: This reaction is unique in that it is under acidic condition in the second step while learners typically encounter strongly basic conditions.

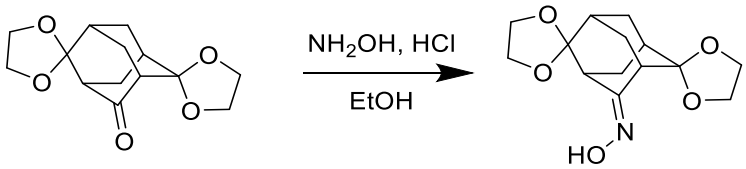
Yousefian, M.; Hashemi, M.; Eskandarpour, V.; Zarghi, A.; Hadizadeh, F.; Ghodsi, R. New Indolin-2-ones, Possessing Sunitinib Scaffold as HDAC Inhibitors and Anti-Cancer Agents with Potential VEGFR Inhibition Activity: Design, Synthesis and Biological Evaluation. *Bioorg. Chem.* **2025**, *156*, 108231. https://doi.org/10.1016/j.bioorg.2025.108231

8b.2.2



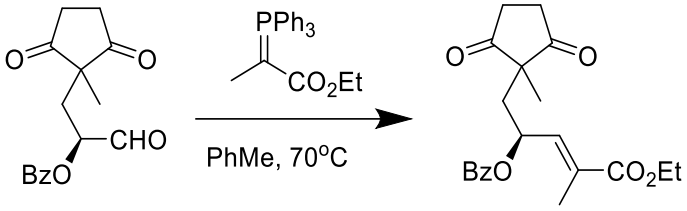
Champciaux, B.; Jamey, N.; Figadère, B.; Ferrié, L. Peroxycarbenium-Mediated Asymmetric Synthesis of 1,2-Dioxanes and 1,2-Dioxolanes. *J. Am. Chem. Soc.* **2025**, *147* (4), 3353–3359. https://doi.org/10.1021/jacs.4c13899

8b.2.3



Ling, Y.; Zhang, P.; Sun, L.; Lai, W.; Luo, J. Efficient Synthesis of 2,2,4,4,6,6-Hexanitroadamantane under Mild Conditions. *Synthesis* **2014**, *46* (16), 2225–2233. https://doi.org/10.1055/s-0033-1341251

8b.2.4



Kuwabara, M.; Matsuo, A.; Kamo, S.; Matsuzawa, A.; Sugita, K. Stereoselective Convergent Synthesis of Carbon Skeleton of Cotylenin A Aglycone. *Synthesis* **2021**, *53* (12), 2092–2102. https://doi.org/10.1055/s-0040-1706684

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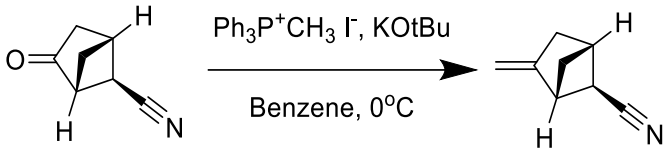

Mehta, G.; Singh, S. R.; Balanarayan, P.; Gadre, S. R. Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]Hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects. *Org. Lett.* **2002**, *4* (14), 2297–2300. https://doi.org/10.1021/ol026005d

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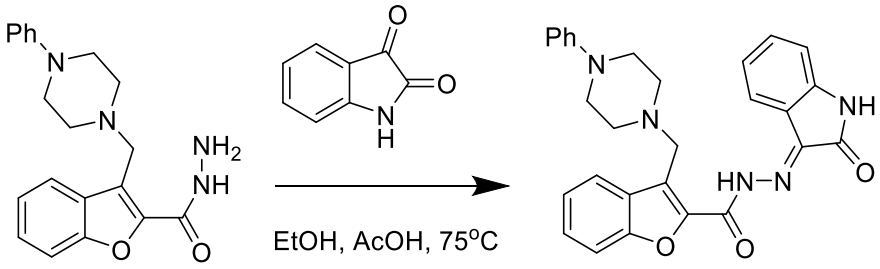
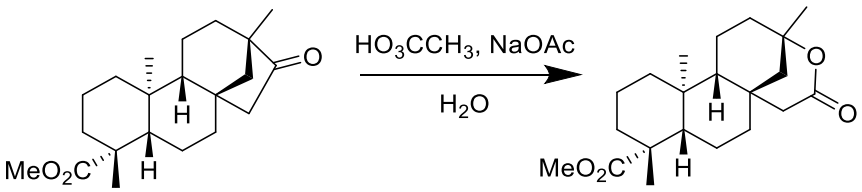


Eldehna, W. M.; Tawfik, H. O.; Nafie, M. S.; Al Kamaly, O.; El-Hamaky, A. A.; El Hassab, M. A.; Elsayed, Z. M.; Elnaggar, Y. S. R.; Al-Karmalawy, A. A.; Di Giacomo, V.; Balaha, M. Novel Benzofuran-Conjugated Indolin-2-ones as Anticancer Agents: Design, Synthesis, Biological Assessments, and Molecular Modeling Insights. *Bioorg. Chem.* **2025**, *160*, 108494. https://doi.org/10.1016/j.bioorg.2025.108494

8b.2.7



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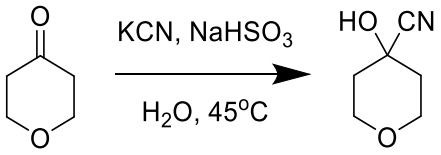
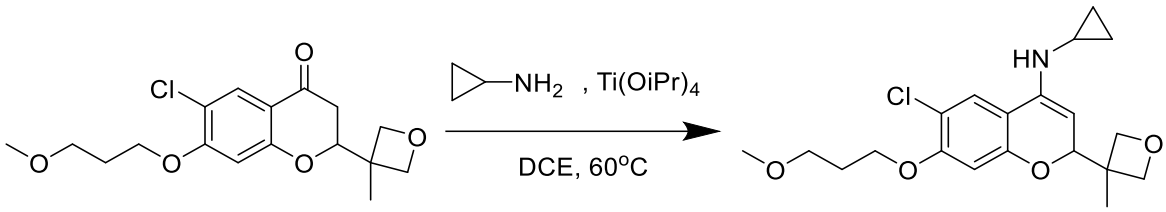
8b.2.8



Holovko-Kamoshenkova, O.; Tošner, Z.; Císařová, I.; Hrdina, R. C–H Amination of Enolizable and Nonenolizable Ketones. *Org. Biomol. Chem.* **2025**, *23* (12), 2818–2822. https://doi.org/10.1039/D5OB00009B

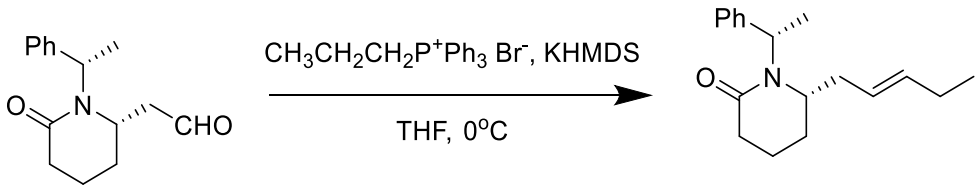
8b.2.9



Hint: $Ti(OiPr)_4$ is used to supply a Lewis acid. In your reaction mechanism, you can use "Ti^{+}" to represent this catalyst.

Mammoliti, O.; Palisse, A.; De Blieck, A.; Joannesse, C.; Allart, B.; Laruelle, C.; Jaunet, A.; De Munck, T.; Van der Plas, S.; Duthion, B.; Catana, C.; Christophe, T.; Houvenaghel, N.; Porte, V.; Jimenez, J.-M.; Beirinckx, F.; Iwens, A.; Chypre, M.; De Rijck, K.; Vandervoort, N.; Nelles, L.; Clément-Lacroix, P.; Delachaume, C.; Belleville, C.; Oste, L.; Borgonovi, M.; Wakselman, E.; Jans, M.; Hue-Perron, J.; Saniere, L.; Brys, R.; Andrews, M. Discovery and Characterization of GLPG3808, a PAPD5/7 Inhibitor for Suppression of Hepatitis B Viral Infections. *J. Med. Chem.* **2026**, *69* (3), 2006-2024. https://doi.org/10.1021/acs.jmedchem.5c01703

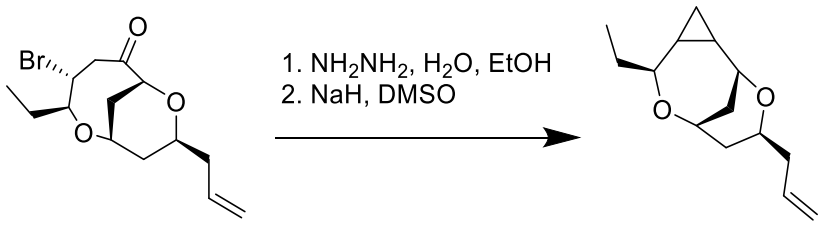
8b.2.10



Nishikawa, K.; Ono, Y.; Mori, S.; Takayama, K.; Ihara, M.; Matsuda, K.; Morimoto, Y. Divergent Nine-Step Syntheses of Perhydrohistrionicotoxin Analogs and Their Inhibition Activity Toward Chicken A4β2-

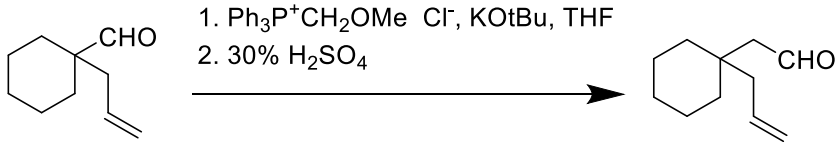
Neuronal Nicotinic Acetylcholine Receptors. *J. Org. Chem.* **2024**, *89* (6), 4128–4133. https://doi.org/10.1021/acs.joc.3c02988

8b.2.11



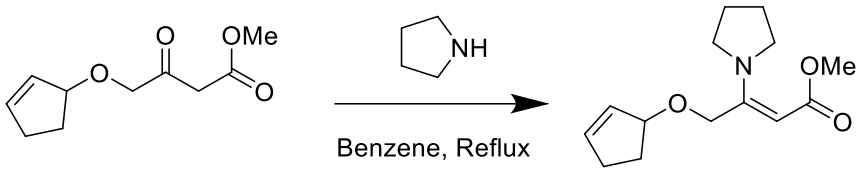
Chan, H. S. S.; Thompson, A. L.; Christensen, K. E.; Burton, J. W. Forwards and Backwards – Synthesis of *Laurencia* Natural Products Using a Biomimetic and Retrobiomimetic Strategy Incorporating Structural Reassignment of Laurefurenynes C–F. *Chem. Sci.* **2020**, *11* (42), 11592–11600. https://doi.org/10.1039/D0SC04120C

8b.2.12



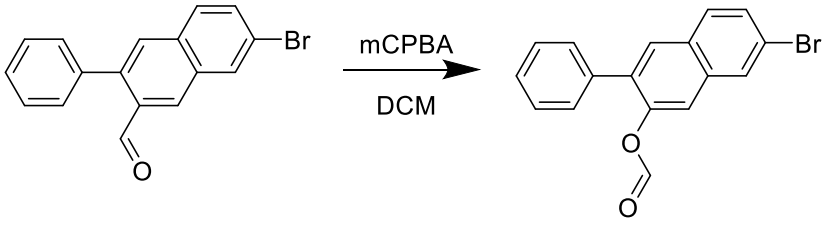
Vulovic, B.; Trmcic, M.; Matovic, R.; Saicic, R. N. Cyclization Reactions of Oxyallyl Cation. A Method for Cyclopentane Ring Formation. *Org. Lett.* **2019**, *21* (23), 9618–9621. https://doi.org/10.1021/acs.orglett.9b03791

8b.2.13



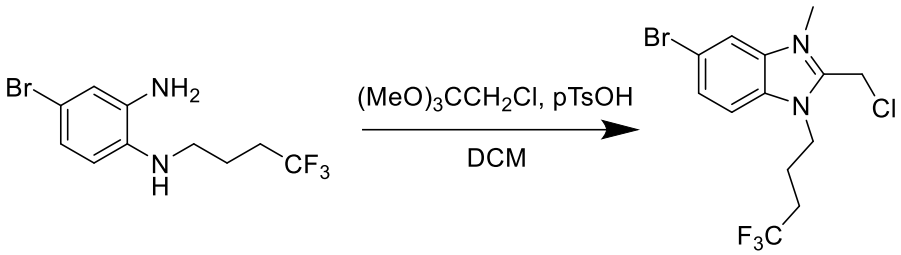
Ho, G.-M.; Tseng, C.-W.; Liu, Y.-H.; Li, Y.-J. Direct Synthesis of 5-Cycloalkene-Substituted γ-Butenolides via [2,3]-Wittig Rearrangement of Vinylogous Urethanes. *Synth. Commun.* **2026**, *56* (4), 318-327. https://doi.org/10.1080/00397911.2026.2621827

8b.2.14



Zhang, C.; Zhang, J.; Lan, Y.; Qin, Y.; Guo, Z.; Zhang, W.; Wang, Q. Photoinduced Polarity-Mismatched Transformations of Isoquinolines into Naphthalenes. *Nat. Commun*. **2026**, *17* (1), 2547. https://doi.org/10.1038/s41467-026-68969-1

8b.2.15

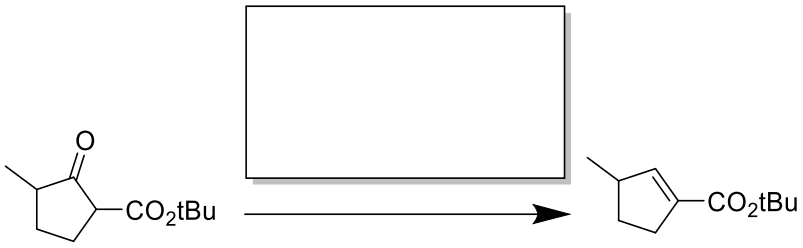


Cao, T. D. C.; Neufeld, K.; Zarate, C.; Nichols, C. J.; Lellek, V.; Deidda, R.; Conza, M.; Schleiss, P.; Rinderhagen, H.; Pye, P.; Muuronen, M.; Chen, W.; Tona, V.; Jouffroy, L.; Viereck, P.; Matcha, K. An Expedient Synthetic Route to the Long-Acting RSV Inhibitor JNJ-6231 via Stereoselective Enzymatic Amination and Regioselective Alkylation. *Org. Process Res. Dev.* **2026**, *30* (1), 121-134. https://doi.org/10.1021/acs.oprd.5c00352

Section 9: Multi-Step Synthesis 1

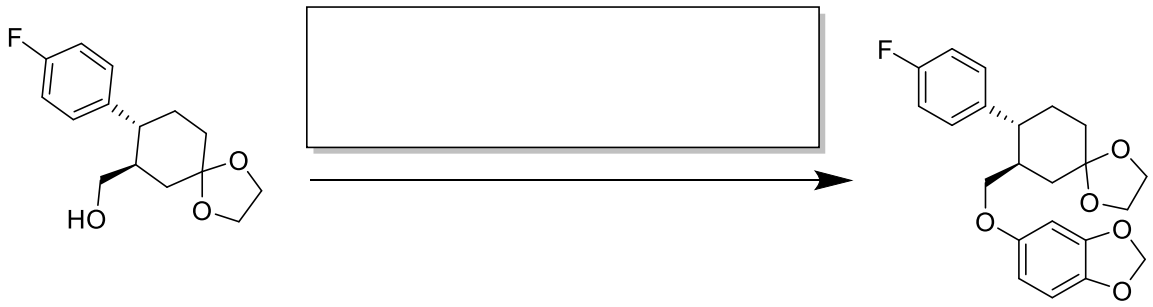
The multistep syntheses presented in this section draw upon fundamental concepts and reactions in Sections 1-8. For each of the questions below, provide reagents that would produce the product indicated from the starting material.

9.1



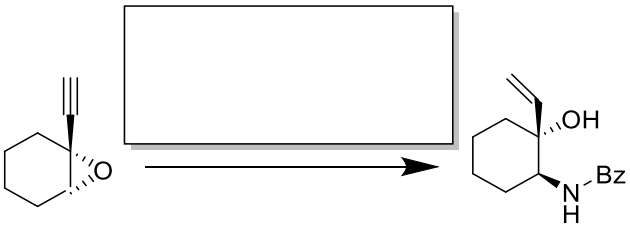
Bunnage, M. E.; Chippindale, A. M.; Davies, S. G.; Parkin, R. M.; Smith, A. D.; Withey, J. M. Asymmetric Synthesis of (1R,2S,3R)-3-Methylcispentacin and (1S,2S,3R)-3-Methyltranspentacin by Kinetic Resolution of *tert*-Butyl (±)-3-Methylcyclopentene-1-carboxylate. *Org. Biomol. Chem.* **2003**, *1* (21), 3698-3707. https://doi.org/10.1039/B306935B

9.2



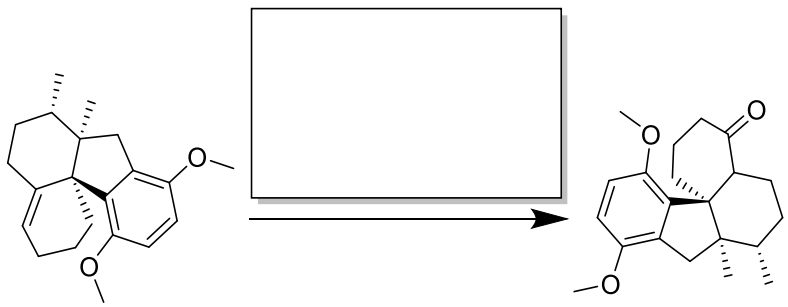
Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in *sp*^{3}-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

9.3



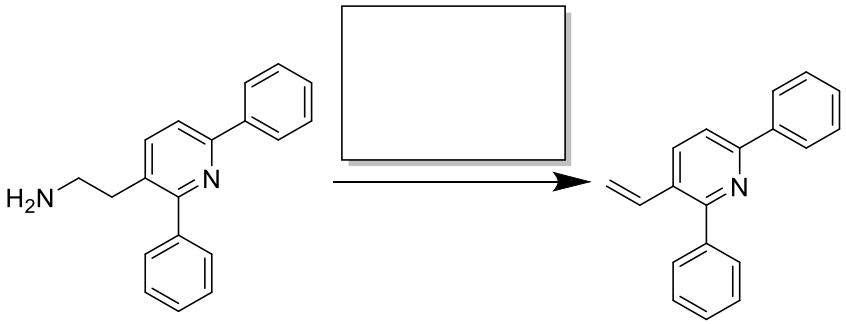
Belov, D. S.; Lukyanenko, E. R.; Kurkin, A. V.; Yurovskaya, M. A. Highly Stereoselective and Scalable Synthesis of *Trans* -Fused Octahydrocyclohepta[*b*]Pyrrol-4(1 *H*)-Ones via the Aza-Cope–Mannich Rearrangement in Racemic and Enantiopure Forms. *J. Org. Chem.* **2012**, *77* (22), 10125–10134. https://doi.org/10.1021/jo301762a

9.4



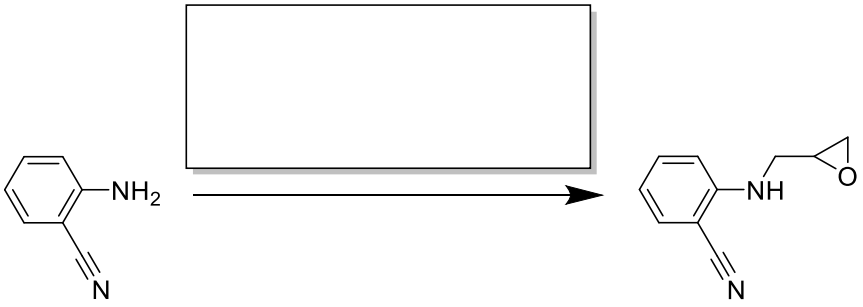
Chong, C.; Chang, L.; Grimm, I.; Zhang, Qunlong; Kuang, Y.; Wang, B.; Kang, J.; Liu, W.; Baars, J.; Guo, Y.; Schmalz, H.-G.; Lu, Z. Divergent Total Synthesis of the Revised Structures of Marine Anti-Cancer Meroterpenoids (+)-Dysiherbols A-E. *Chem. Sci.* **2023**. *14* (12). 3302-3310. https://doi.org/10.1039/d3sc00173c

9.5



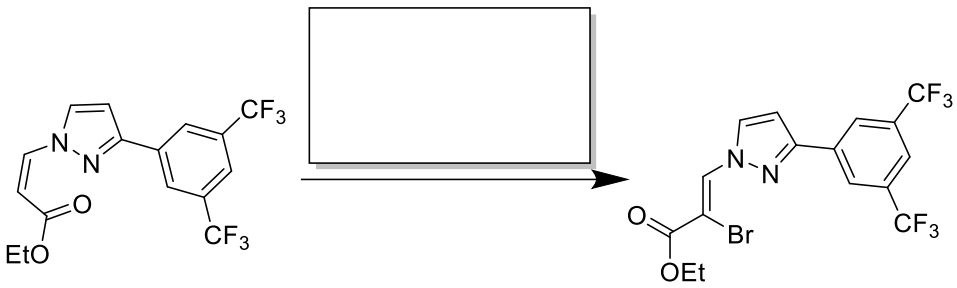
Khardina, P. A.; Buev, E. M.; Moshkin, V. S.; Sosnovskikh, V. Y. Four-Step Synthesis of the β-Pyridylethylamine Core via Ring Opening of Pyrrolidines. *J. Org. Chem.* **2026**, *91* (18), 6279-6293. https://doi.org/10.1021/acs.joc.5c03267

9.6



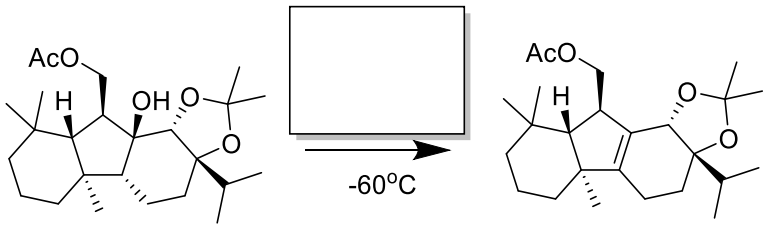
Lee, K.; Lee, X.; Zhou, C.-Y.; Chu, Y.-L.; Lin, C.-K. *Tert* -Butyl Carbonate as a Nucleophile in Epoxide Ring Opening: A Cascade Synthesis of 5-(Hydroxymethyl)Oxazolidin-2-One. *J. Org. Chem.* **2025**, *90* (23), 7976–7981. https://doi.org/10.1021/acs.joc.5c00537

9.7



Miao, H.; Qin, Y.; Shao, D.; Chen, Q.; Pan, Y.; Lei, M.; Wu, R.; Ye, X.; Wang, X.; Zhu, Y. Discovery of SZJK-0421: A Novel Potent, Low Toxicity, Selective Second Generation of CRM1 Inhibitor for the Treatment of Both Hematological and Solid Tumors. *J. Med. Chem.* **2024**, *67* (22), 20595–20618. https://doi.org/10.1021/acs.jmedchem.4c02169

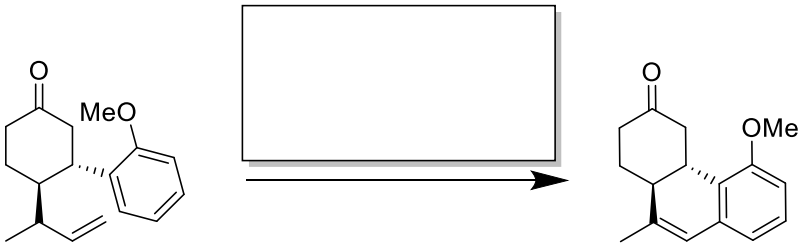
9.8



Note: You will learn later that this structure contains acid-sensitive functional groups, so acidic conditions should be avoided.

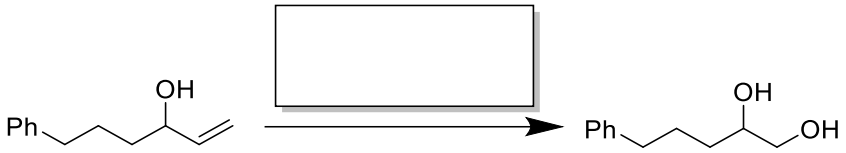
Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. Enantioselective Total Synthesis of Cytotoxic Taiwaniaquinones A and F. *Chem. Commun.* **2010**, *46* (48), 9244. https://doi.org/10.1039/c0cc03763j

9.9



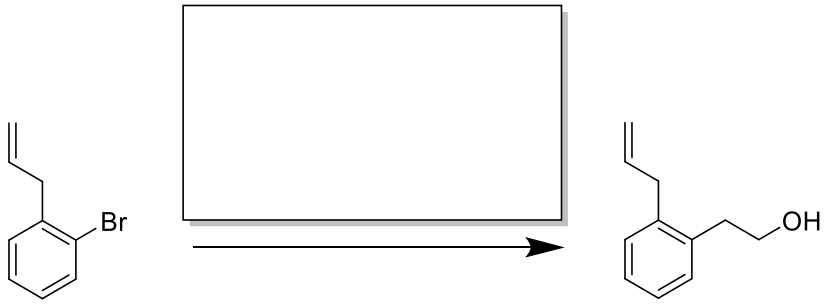
Roosen, P. C.; Karns, A. S.; Ellis, B. D.; Vanderwal, C. D. Evolution of a Short and Stereocontrolled Synthesis of (+)-7,20-Diisocyanoadociane. *J. Org. Chem.* **2022**, *87* (2), 1398–1420. https://doi.org/10.1021/acs.joc.1c02700

9.10



Liu, Z.; Breit, B. Rhodium-Catalyzed Regioselective Addition of *N* -Hydroxyl Imides to Internal Alkynes. *Isr. J. Chem.* **2026**, *66* (3), e70014. https://doi.org/10.1002/ijch.70014

9.11



Wang, Y.; Hong, F.; Robertson, C. M.; Mudd, R. J.; Bower, J. F. Iridium-Catalyzed Stereoselective α-Alkylation of α-Hydroxy Ketones with Minimally Polarized Alkenes. *J. Am. Chem. Soc*. **2026**, *148* (4), 3911–3917. https://doi.org/10.1021/jacs.5c19724

Section 10a: Carboxylic Acids and Derivatives 1

Required foundation for this section:

Nucleophilic acyl substitution

Interconversion of carboxylic acid to and from its derivatives

Transesterification

Saponification

Aminolysis

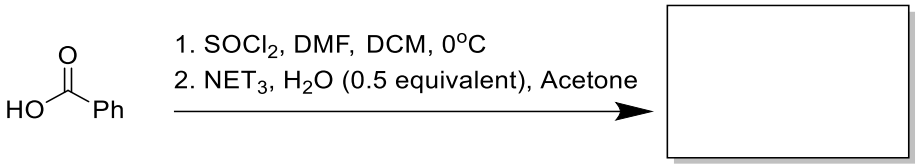
Esterification

Full and partial reduction of carboxylic acids and esters

Section 10a – Box-Type Questions

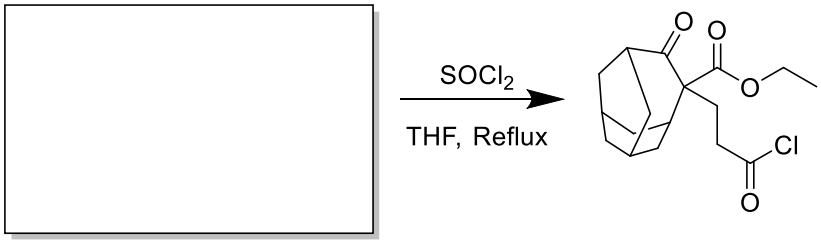
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

10a.1.1



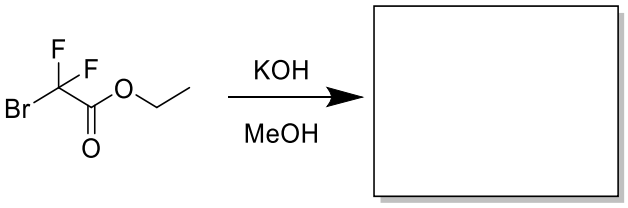
Herington, F.; Achal, F. J.; Figueroa-Agosto, D.; Liu, C.; Ge, H. Regioselective Pd-Catalyzed C1–H Acylation of Carbazoles via Pd/Norbornene Cooperative Catalysis. *J. Org. Chem*. **2025**, *90* (35), 12485–12489. https://doi.org/10.1021/acs.joc.5c01838

10a.1.2



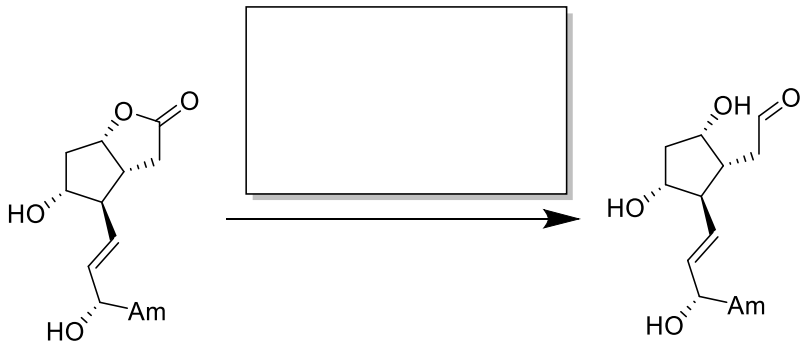
Tkachenko, I. M.; Mankova, P. A.; Rybakov, V. B.; Golovin, E. V.; Klimochkin, Y. N. Wagner–Meerwein Type Rearrangement in 5-Oxohomoadamantane Series. *Org. Biomol. Chem.* **2020**, *18* (3), 465–478. https://doi.org/10.1039/C9OB02060H

10a.1.3



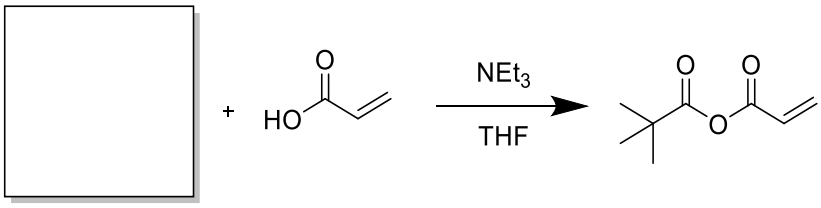
Pounder, A.; Lilienthal, E. O.; Solorzano, J. D.; Wetmore, S. D.; Hamel, J.-D. Structural Characterization of Difluoroglycine Betaines. *J. Mol. Struct*. **2026**, *1368*, 146292. https://doi.org/10.1016/j.molstruc.2026.146292

10a.1.4



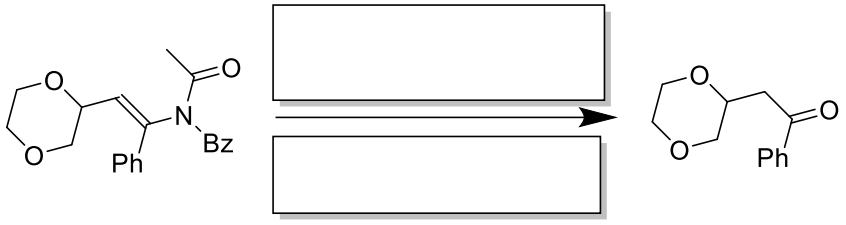
Yin, Y.; Wang, J.; Li, J. A Concise and Scalable Chemoenzymatic Synthesis of Prostaglandins. *Nat. Commun.* **2024**, *15* (1), 2523. https://doi.org/10.1038/s41467-024-46960-y

10a.1.5



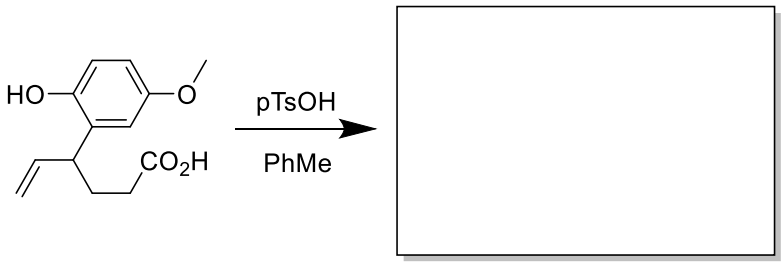
Zhong, X.; Yu, Z.; Meng, R.; Gong, Y.; Li, J.; He, W.; Li, H.; Li, J.; Wu, Z.; Duan, Q.; Li, Y.; Liu, Y.; Peng, Z.; Song, D. Synthesis and Evolution of 16-Membered Macrolide Carrimycin Derivatives as a Novel Class of Anti-HCoV-OC43 Agents Targeting Viral FSE RNA. *Eur. J. Med. Chem.* **2025**, *287*, 117373. https://doi.org/10.1016/j.ejmech.2025.117373

10a.1.6



Han, J.; Zhang, Q.-R.; Wang, Y.-L.; Lu, X.-Y.; Zeng, L.-L.; Li, Y.-Q.; Chen, F.-E. Visible-Light Induced Dehydrogenative Cross-Coupling of Enamides with Hydrocarbons Enabled by Aryl Thianthrenium Salt. *Org. Lett.* **2026**, *28* (14), 4518–4523. https://doi.org/10.1021/acs.orglett.6c00763

10a.1.7



Ikonnikova, V. A.; Solyev, P. N.; Al Mufti, A. M.; Kungurtsev, K. D.; Korlyukov, A. A.; Baranov, M. S.; Mikhaylov, A. A. Synthesis of Chroman Derivatives by Group Transposition and Atom Swapping in 1-Tetralones: Single-Atom Editing Enabled by Oxidative Ring Contraction of Benzoxepine Silyl Ketene Acetals. *Angew. Chem. Int. Ed.* **2025**, *64* (31), e202506564. https://doi.org/10.1002/anie.202506564

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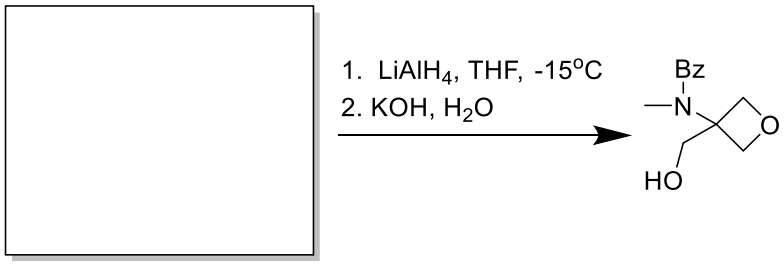

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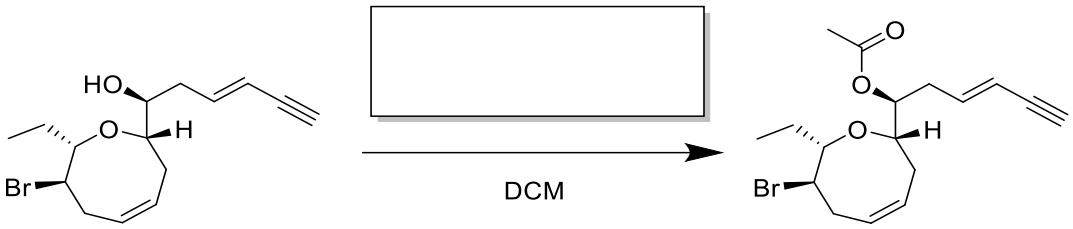

Chan, H. S. S.; Thompson, A. L.; Christensen, K. E.; Burton, J. W. Forwards and Backwards – Synthesis of *Laurencia* Natural Products Using a Biomimetic and Retrobiomimetic Strategy Incorporating Structural Reassignment of Laurefurenynes C–F. *Chem. Sci.* **2020**, *11* (42), 11592–11600. https://doi.org/10.1039/D0SC04120C

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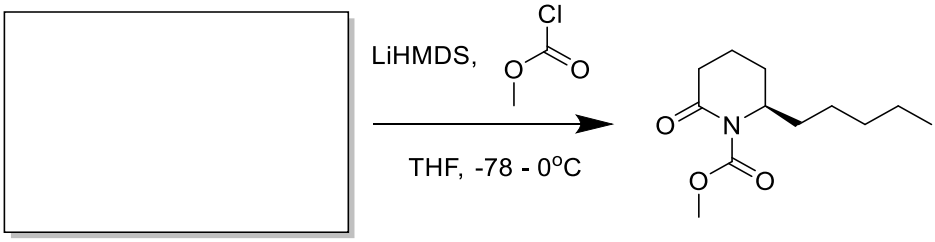

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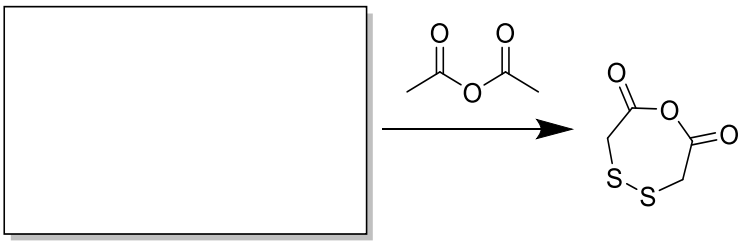

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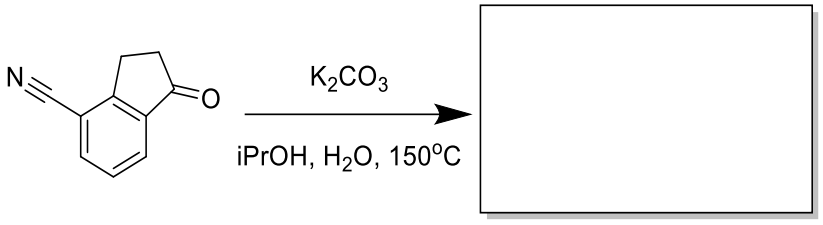

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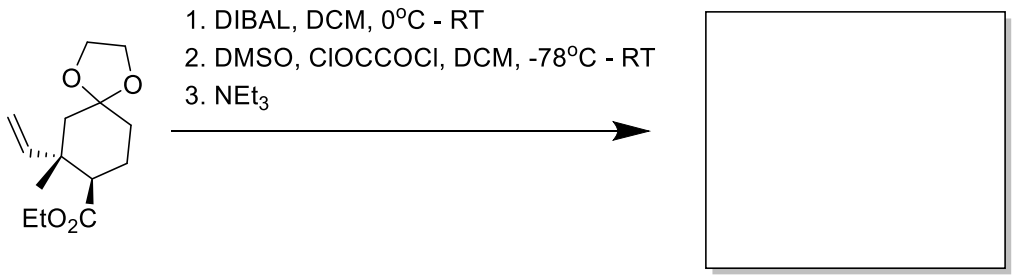

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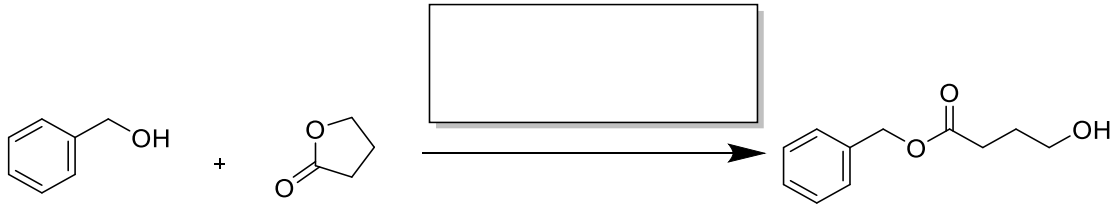

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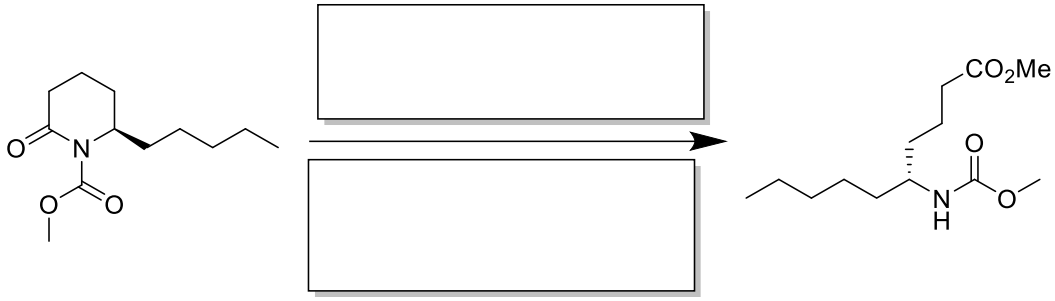

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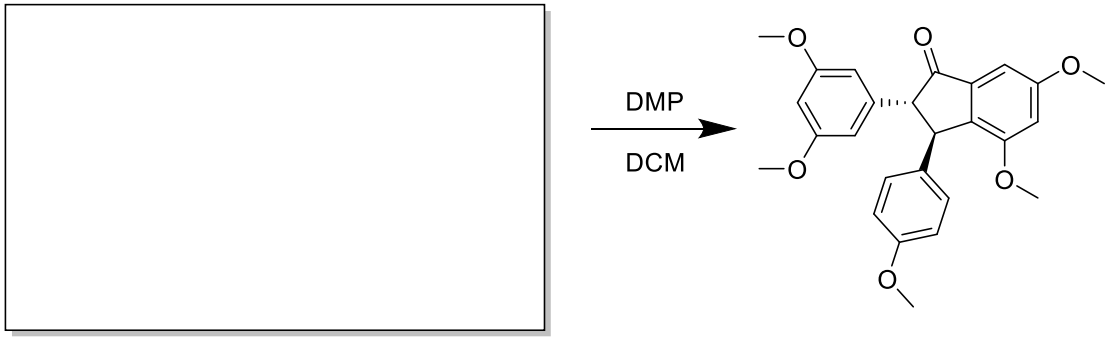

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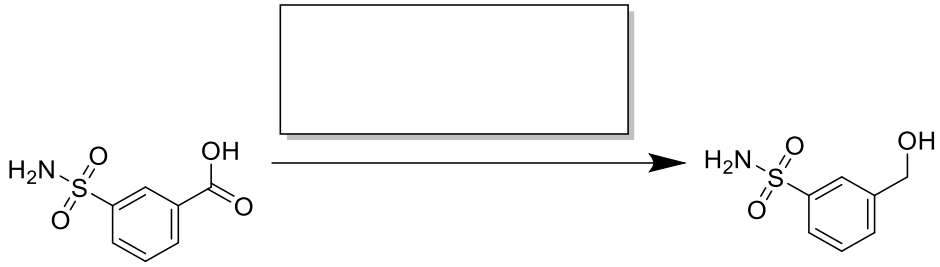

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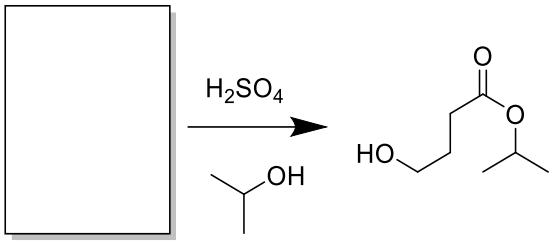

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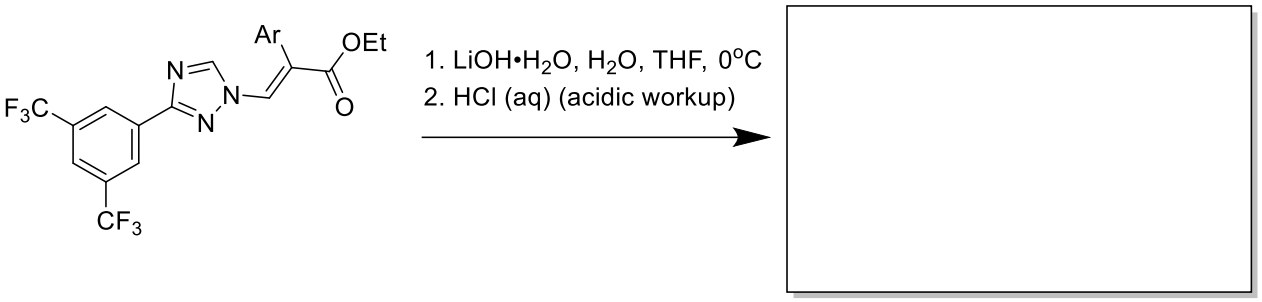

Miao, H.; Qin, Y.; Shao, D.; Chen, Q.; Pan, Y.; Lei, M.; Wu, R.; Ye, X.; Wang, X.; Zhu, Y. Discovery of SZJK-0421: A Novel Potent, Low Toxicity, Selective Second Generation of CRM1 Inhibitor for the Treatment of Both Hematological and Solid Tumors. *J. Med. Chem.* **2024**, *67* (22), 20595–20618. https://doi.org/10.1021/acs.jmedchem.4c02169

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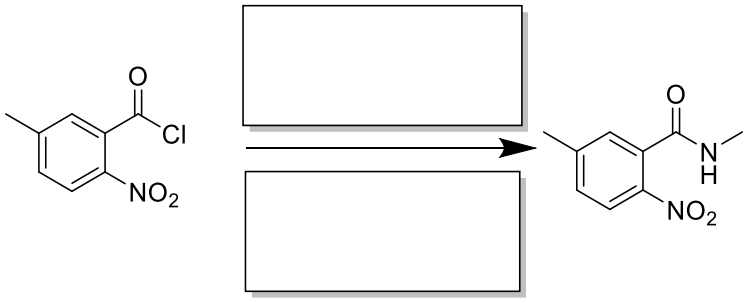

Chen, Y.; Liu, X.; Shi, W.; Zheng, S.; Wang, G.; He, L. One-Pot Synthesis of Seven-Membered Heterocyclic Derivatives of Diazepines Involving Copper-Catalyzed Rearrangement Cascade Allyl-Amination. *J. Org. Chem*. **2020**, *85* (8), 5146–5157. https://doi.org/10.1021/acs.joc.9b02710

Section 10a – Mechanism Questions

Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

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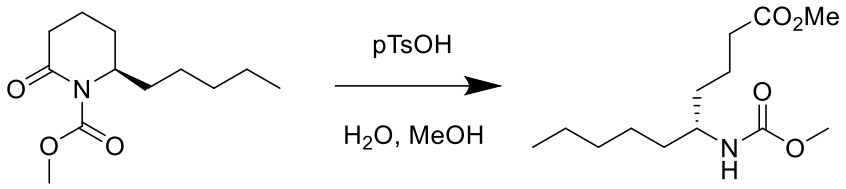

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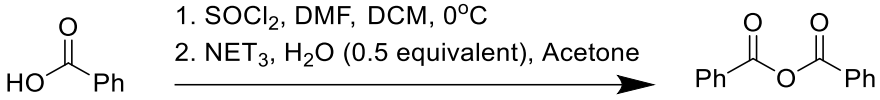

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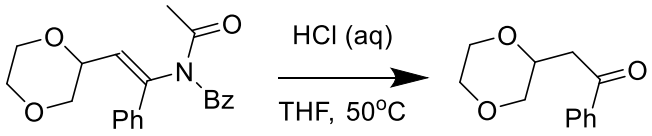

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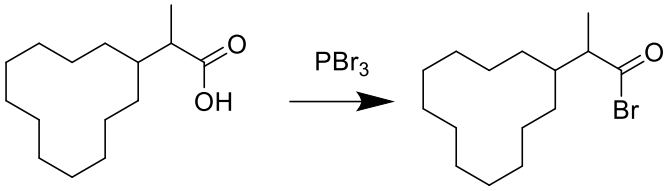

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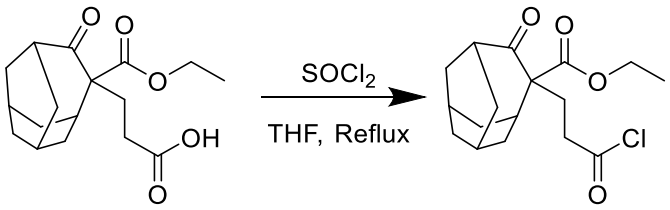

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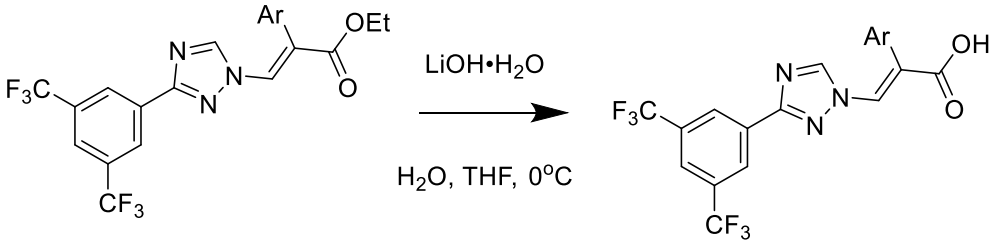

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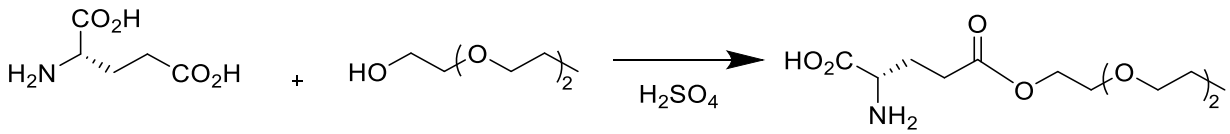

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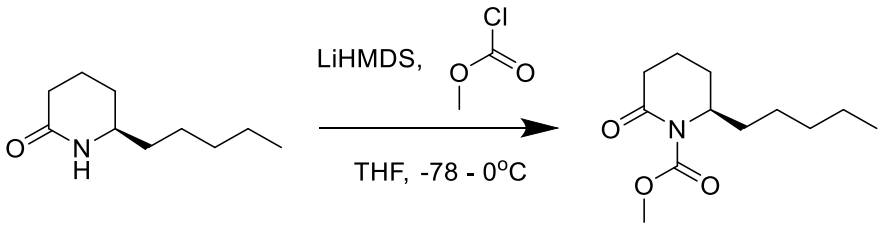

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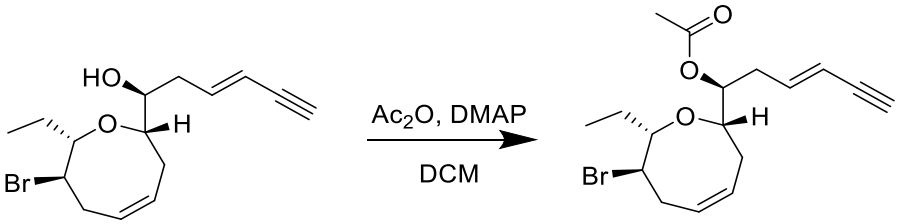

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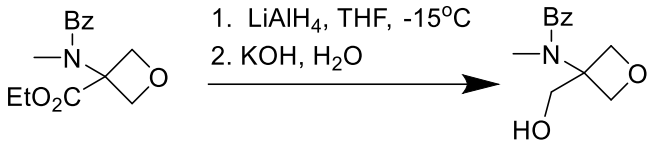

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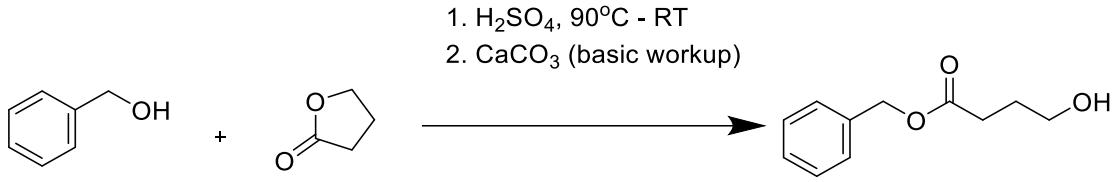

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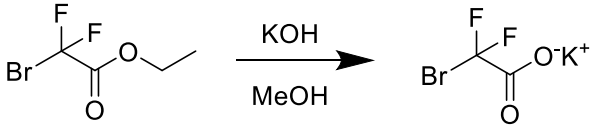

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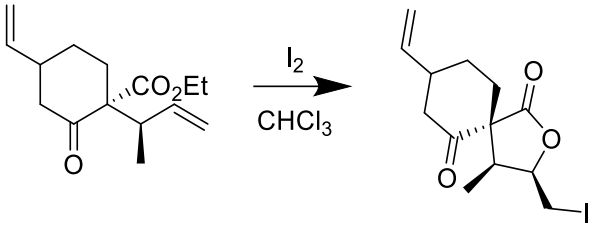

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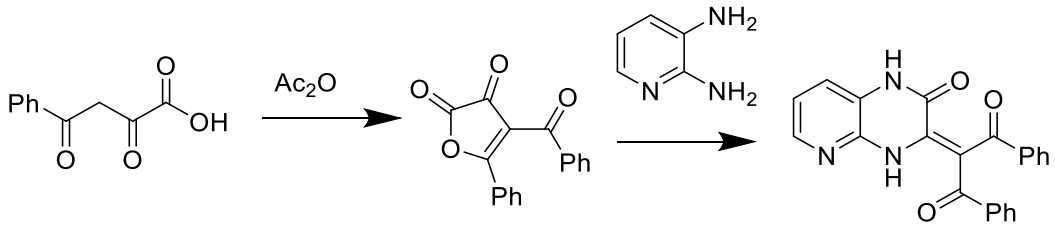

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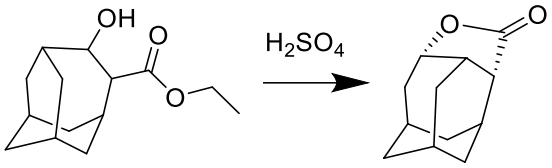

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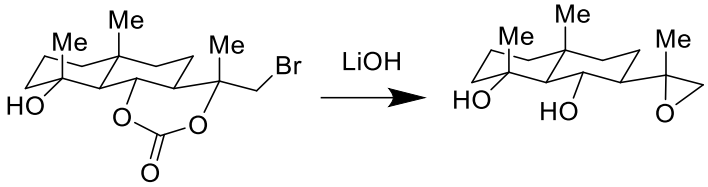

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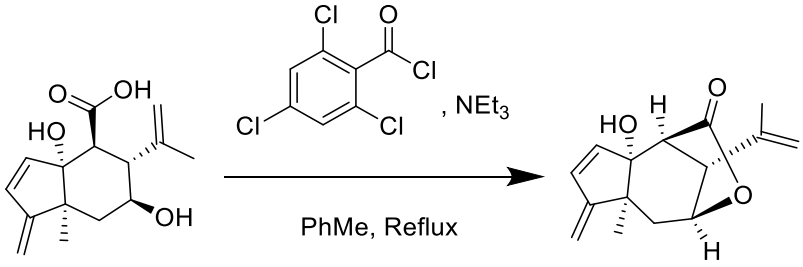

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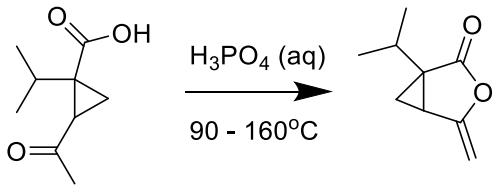

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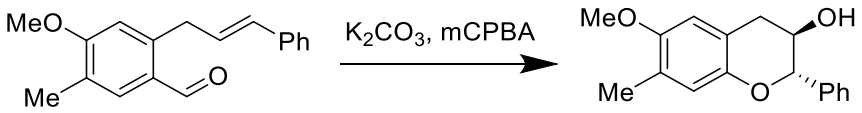

Chang, M.-Y.; Hsiao, Y.-T.; Lai, K.-H. *m*CPBA-Mediated Intramolecular Oxidative Annulation of *ortho*-Crotyl or Cinnamyl Arylaldehydes: Synthesis of Benzofused Five-, Six-, and Seven-Membered Oxacycles. *J. Org. Chem.* **2018**, *83* (22), 14110-14119. https://doi.org/10.1021/acs.joc.8b02146

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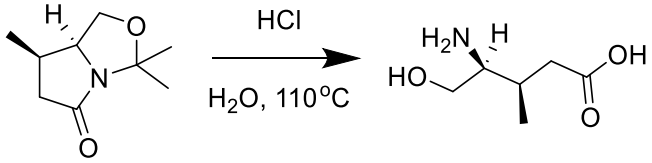

Shi, H.; Song, Y.; Gong, H. Facile Preparation of Chiral 1,2-Amino Alcohols Containing Unsymmetrical *N*-α-Secondary Alkyl Substituents. *Synlett* **2026**, *37* (2), 269-274. https://doi.org/10.1055/a-2711-1520

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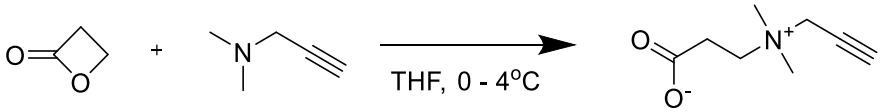

Li, N.; Liu, Z.; Mysona, J.; Shan, N.; Strzalka, J.; de Pablo, J. J.; Wang, S. Solid-State Side-Chain Functionalization of Conjugated Polymers for Expanded Chemical and Functional Versatility. *J. Am. Chem. Soc.* **2026**, *148* (9), 9803–9811. https://doi.org/10.1021/jacs.5c21851

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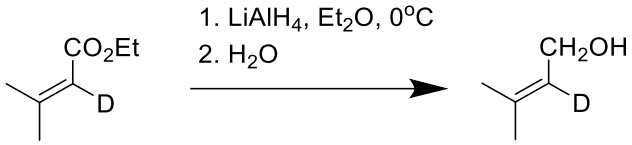

Chen, Y.; Liu, X.; Shi, W.; Zheng, S.; Wang, G.; He, L. One-Pot Synthesis of Seven-Membered Heterocyclic Derivatives of Diazepines Involving Copper-Catalyzed Rearrangement Cascade Allyl-Amination. *J. Org. Chem*. **2020**, *85* (8), 5146–5157. https://doi.org/10.1021/acs.joc.9b02710

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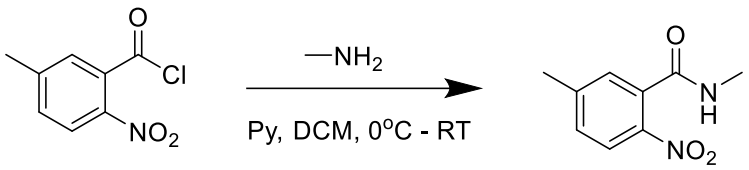

Chen, Y.; Liu, X.; Shi, W.; Zheng, S.; Wang, G.; He, L. One-Pot Synthesis of Seven-Membered Heterocyclic Derivatives of Diazepines Involving Copper-Catalyzed Rearrangement Cascade Allyl-Amination. *J. Org. Chem*. **2020**, *85* (8), 5146–5157. https://doi.org/10.1021/acs.joc.9b02710

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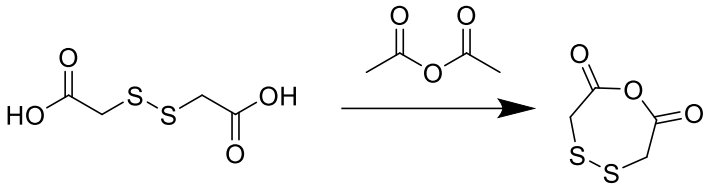


Wang, D.; Xu, S.; Zheng, S.; et al. Phospholipid-Like Prodrug Liposomes with High Drug-Carrier Affinity and High Tumor Selectivity: Strong Competitors of Paclitaxel Nanomedicines. *Adv. Funct. Mater*. **2026**, *36* (1), e02341. https://doi.org/10.1002/adfm.202502341

Section 10b: Carboxylic Acids and Derivatives 2

Required foundation for this section:

Reduction and hydrolysis of nitriles

Reduction of amides

Grignard reagents with esters

Organocuprates with acid chlorides

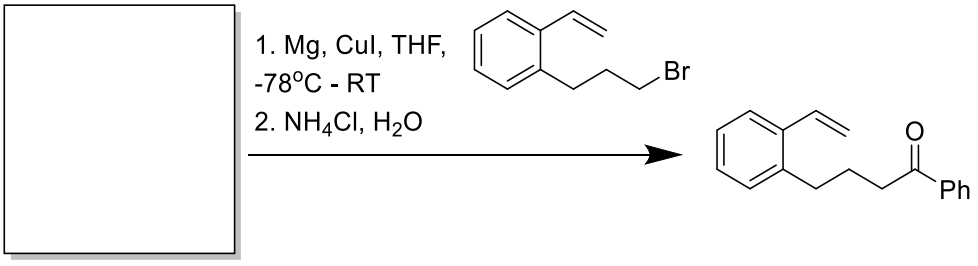
A Note on Grignard Reagents

The literature frequently reports the use of additional salts to accelerate Grignard reagent formation, increase Grignard reagent reactivity, improve chemoselectivity in the presence of competing functional groups, or enhance the reactivity of carbonyl compounds. For an introductory organic chemistry course, the specific role of these additives is typically beyond the scope of the material. Nevertheless, learners should consult their instructor if further clarification is required.

Section 10b – Box-Type Questions

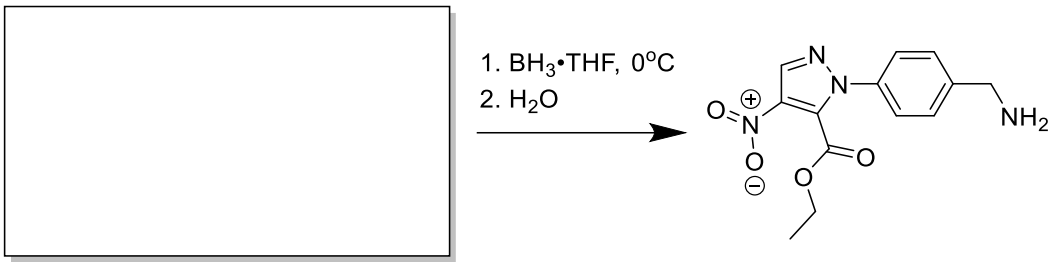
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

10b.1.1



Petrone, D. A.; Malik, H. A.; Clemenceau, A.; Lautens, M. Functionalized Chromans and Isochromans via a Diastereoselective Pd(0)-Catalyzed Carboiodination. *Org. Lett*. **2012**, *14* (18), 4806–4809. https://doi.org/10.1021/ol302111y

10b.1.2



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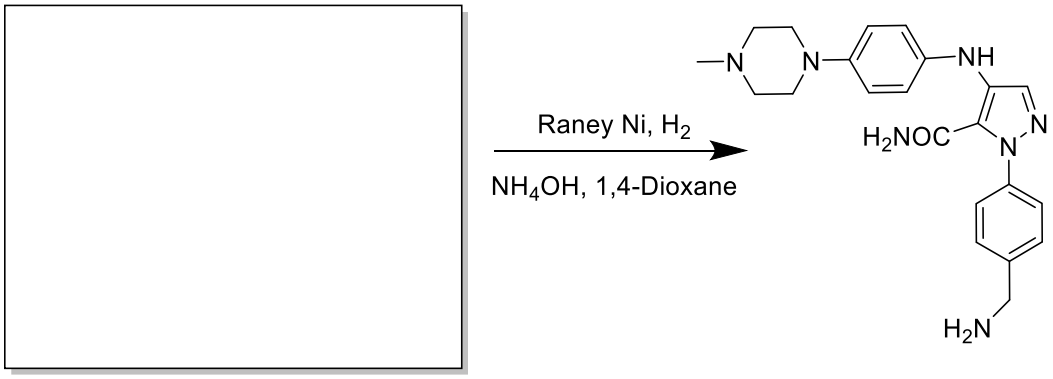

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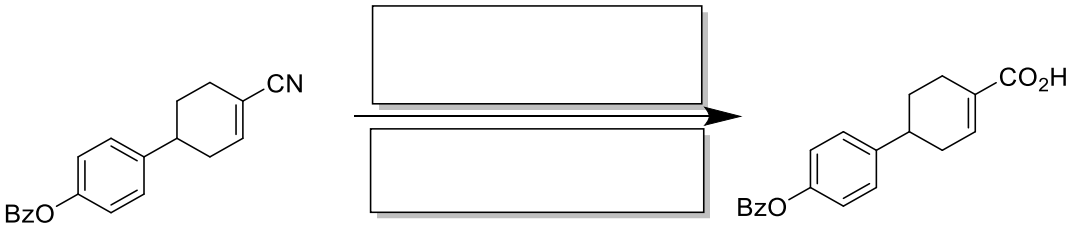

Amatya, E.; Subramanian, C.; Long, R.; McNamara, K.; Cohen, M. S.; Blagg, B. S. J. The Investigation of Hsp90C-Terminal Inhibitors Containing Amide Bioisosteres. *ChemMedChem* **2024**, *19* (24), e202400418. https://doi.org/10.1002/cmdc.202400418

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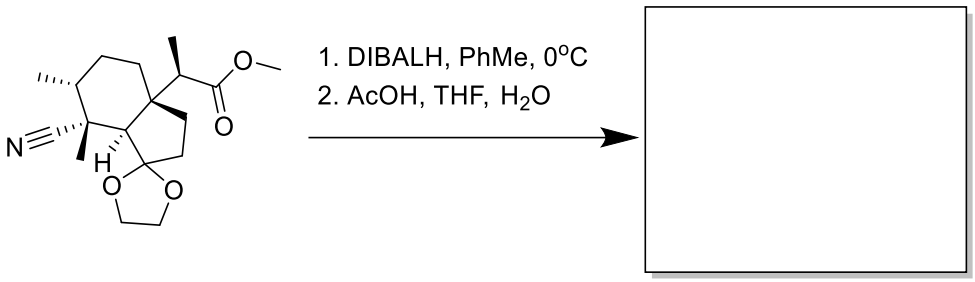

Note: Under the conditions provided, the ester group is not reduced.

Goethe, O.; DiBello, M.; Herzon, S. B. Total Synthesis of Structurally Diverse Pleuromutilin Antibiotics. *Nat. Chem.* **2022**, *14* (11), 1270-1277. https://doi.org/10.1038/s41557-022-01027-7

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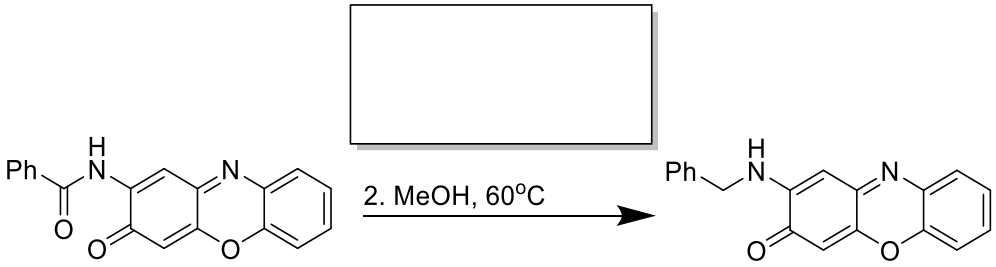

Xu, M.; Xu, L.; Wang, B.; Zhang, W.; Wang, L.; Wang, A.; Lu, Y. Discovery and Optimization of Phenoxazinone Derivatives as Potent Antitubercular Agents Targeting FabD Protein. *J. Med. Chem.* **2025**, acs.jmedchem.5c02148. https://doi.org/10.1021/acs.jmedchem.5c02148

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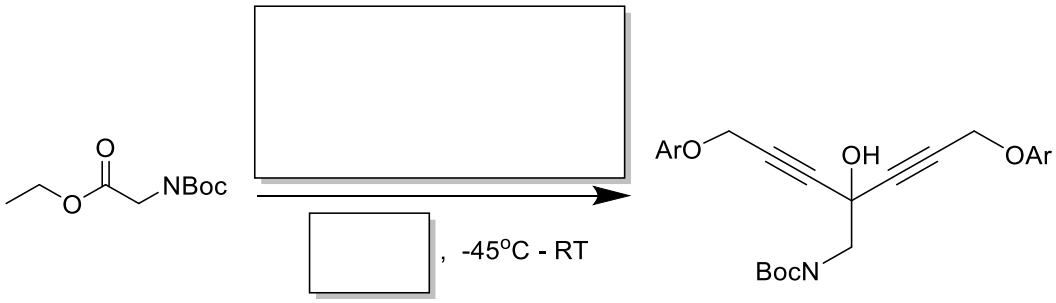

Solas, M.; Renedo, L.; Suárez-Pantiga, S.; Sanz, R. Synthesis of 4-Furan- and 4-Pyrrol-3-yl-2H-chromenes from Naturally-Occurring Compounds by Gold(I)-Catalyzed Domino Reactions. *Adv. Synth. Catal*. **2023**, *365*, 2049–2058. https://doi.org/10.1002/adsc.202300307

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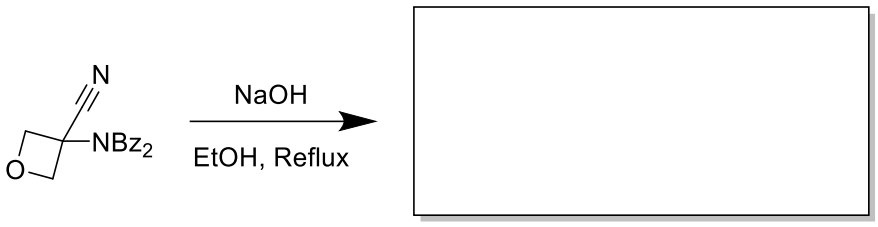

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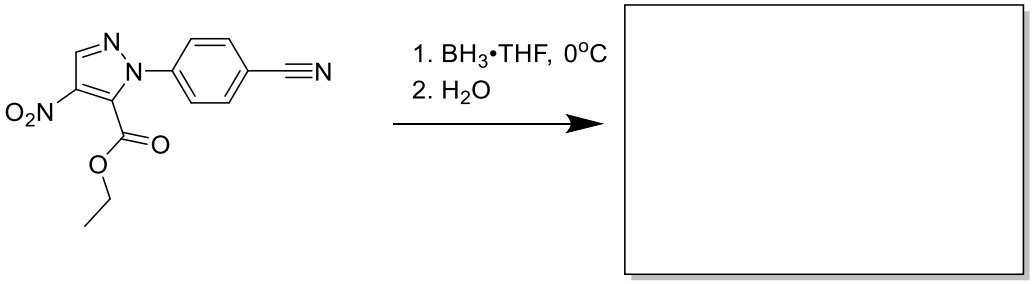

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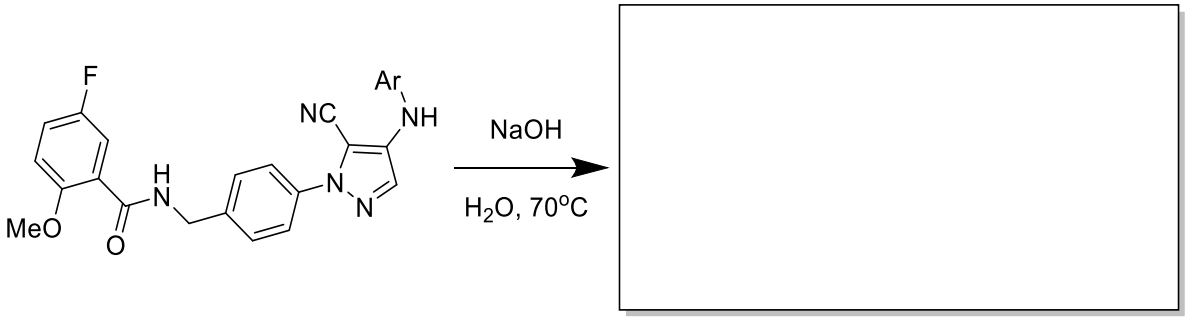

Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2026**, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

10b.1.11



Chen, L.; Liao, G.; Liu, B. Ligand-Enabled Nickel(II)-Catalyzed β-C(sp^3^)–H Thiolation of Ketones. *Org. Lett*. **2024**, *26* (42), 9103–9107. https://doi.org/10.1021/acs.orglett.4c03404

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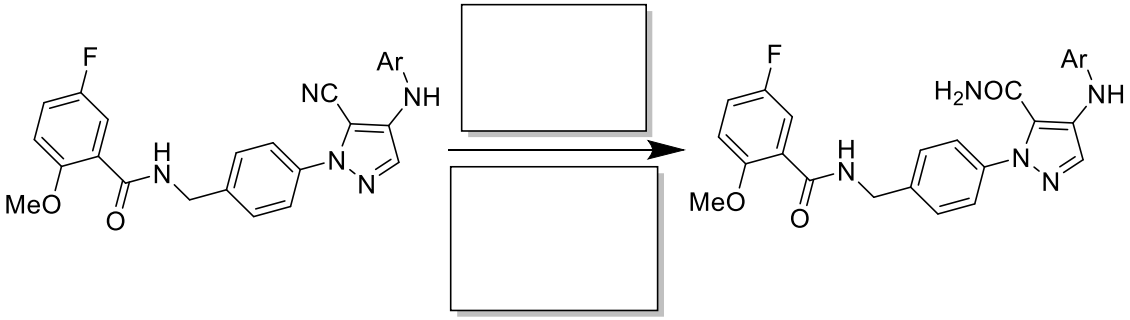

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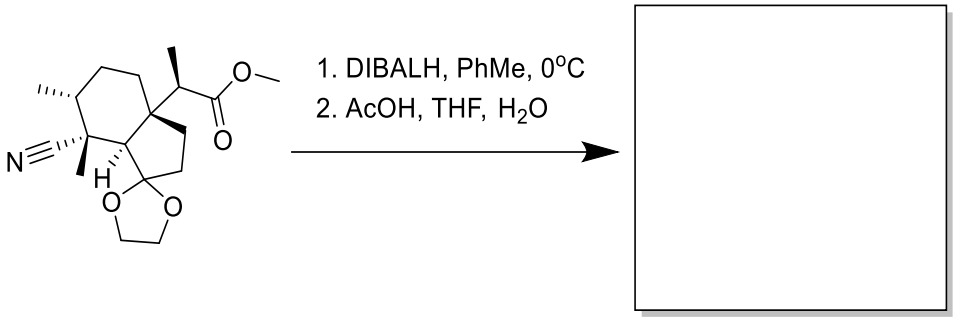

Goethe, O.; DiBello, M.; Herzon, S. B. Total Synthesis of Structurally Diverse Pleuromutilin Antibiotics. *Nat. Chem.* **2022**, *14* (11), 1270-1277. https://doi.org/10.1038/s41557-022-01027-7

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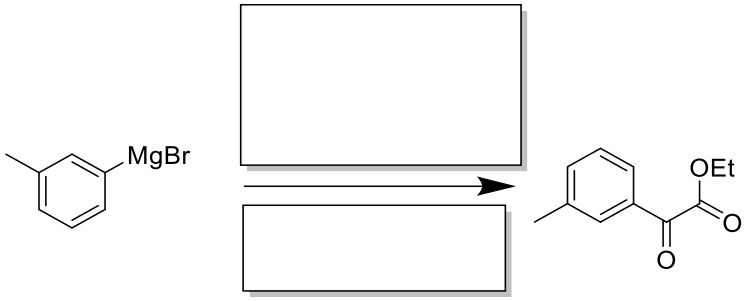

Yang, Y.-C.; Li, W.-S.; Uang, T.-Y.; Kuo, T.-S.; Wu, H.-L. Access to Chiral Tertiary α-Hydroxyesters via Rhodium-Catalyzed Enantioselective Allylation of α-Ketoesters. *Chem. Asian J*. **2026**, *21* (2), e70585. https://doi.org/10.1002/asia.70585

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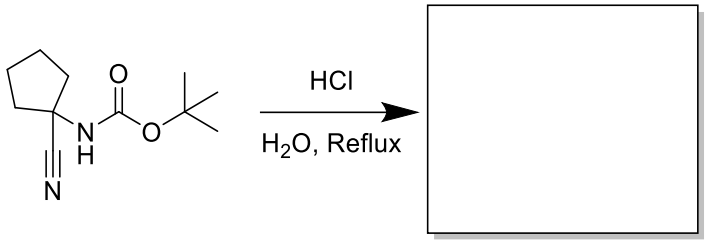

Zhang, Y.-H.; Jiao, F.-N.; Cao, F.-Y.; Zhao, M.-Z.; Sun, B.-Y.; Zhou, M.-J.; Xiao, H.; Dai, J.-J. Practical and Direct Synthesis of α-Aminonitriles Using N-Boc-O-tosyl Alkylhydroxylamines and TMSCN. *Chem. Commun*. **2026**, *62* (66), 16531–16535. https://doi.org/10.1039/D6CC03609K

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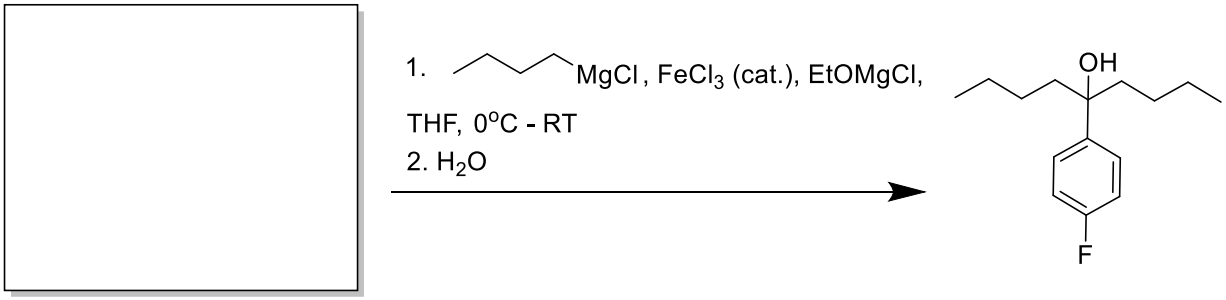

Cahiez, G.; Lefèvre, G.; Moyeux, A.; Guerret, O.; Gayon, E.; Guillonneau, L.; Lefèvre, N.; Gu, Q.; Zhou, E. Gram-Scale, Cheap, and Eco-Friendly Iron-Catalyzed Cross-Coupling between Alkyl Grignard Reagents and Alkenyl or Aryl Halides. *Org. Lett*. **2019**, *21* (8), 2679–2683. https://doi.org/10.1021/acs.orglett.9b00665

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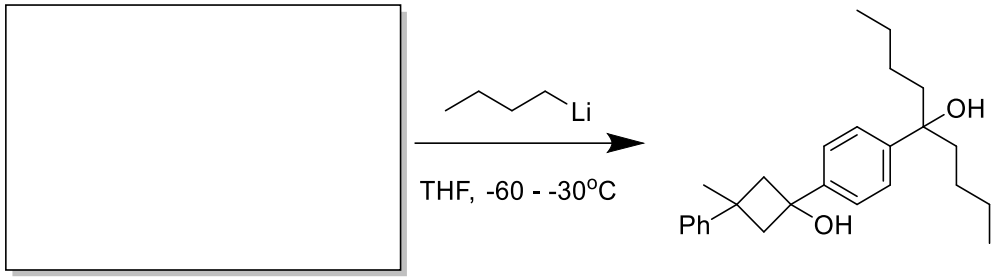

Note: The authors used butyl lithium instead of a Grignard reagent.

Parra-García, S.; Ballester-Ibáñez, M.; García-López, J.-A. Pd-Catalyzed Formal [2 + 2]-Retrocyclization of Cyclobutanols via 2-Fold Csp^3^−Csp^3^ Bond Cleavage. *J. Org. Chem*. **2024**, *89* (2), 882–886. https://doi.org/10.1021/acs.joc.3c01750

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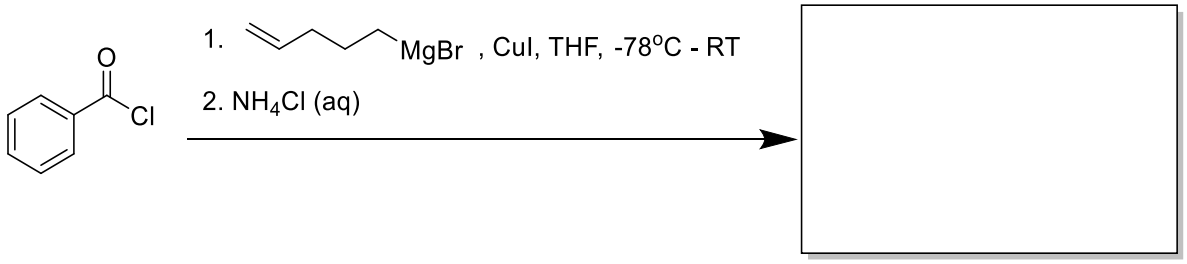

Wang, Y.; Hong, F.; Robertson, C. M.; Mudd, R. J.; Bower, J. F. Iridium-Catalyzed Stereoselective α-Alkylation of α-Hydroxy Ketones with Minimally Polarized Alkenes. *J. Am. Chem. Soc*. **2026**, *148* (4), 3911–3917. https://doi.org/10.1021/jacs.5c19724

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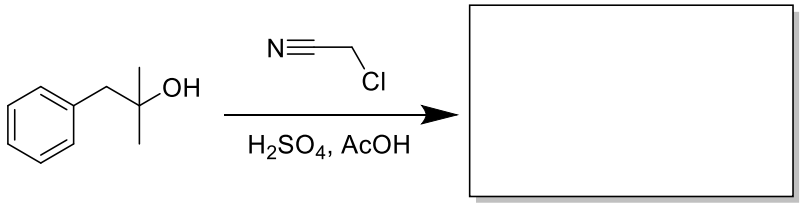
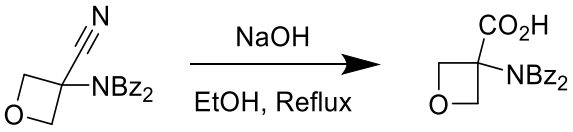


Enudi, O. C.; Twitty, J. C.; Rotella, M. E.; Underwood, S. J.; Kozlowski, M. C.; Watson, M. P. Pyridinium Design for Deaminative Reactions of Sterically Encumbered Alkyl Amines. *Org. Lett*. **2026**, *28* (22), 7009–7014. https://doi.org/10.1021/acs.orglett.6c01717

Section 10b – Mechanism Questions

Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

10b.2.1



Litskan, E. V.; Lynnyk, S. V.; Shypov, R. H.; Vashchenko, B. V.; Hoida, A. Ye.; Klymenko-Ulianov, O. O.; Gorlova, A. O.; Granat, D. S.; Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V. Fine-Tuning of Physicochemical Properties of 3,3-Disubstituted Oxetanes Introducing Fluorine Atom(s) on the Building Blocks Level. *Chem. Eur. J.* **2025**, *31* (51), e202500940. https://doi.org/10.1002/chem.202500940

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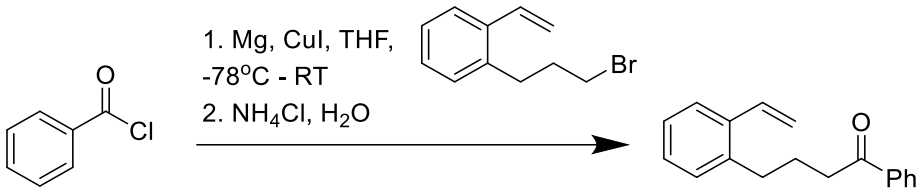

Petrone, D. A.; Malik, H. A.; Clemenceau, A.; Lautens, M. Functionalized Chromans and Isochromans via a Diastereoselective Pd(0)-Catalyzed Carboiodination. *Org. Lett*. **2012**, *14* (18), 4806–4809. https://doi.org/10.1021/ol302111y

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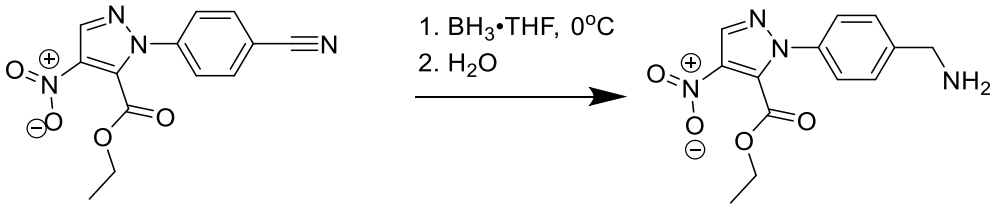

Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2026**, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

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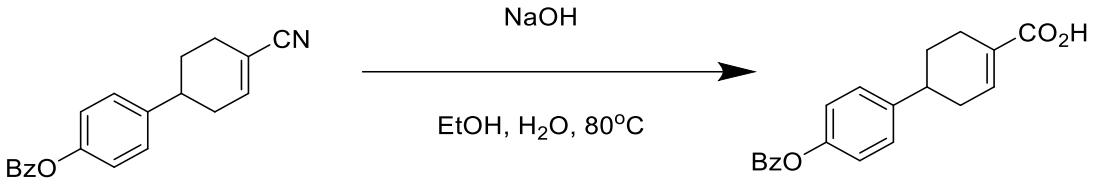

Amatya, E.; Subramanian, C.; Long, R.; McNamara, K.; Cohen, M. S.; Blagg, B. S. J. The Investigation of Hsp90C-Terminal Inhibitors Containing Amide Bioisosteres. *ChemMedChem* **2024**, *19* (24), e202400418. https://doi.org/10.1002/cmdc.202400418

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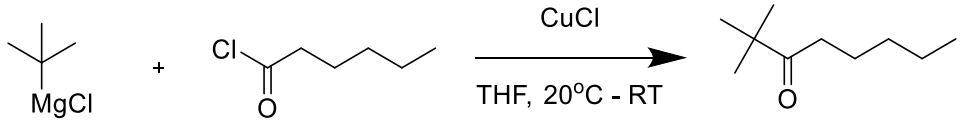

Chen, L.; Liao, G.; Liu, B. Ligand-Enabled Nickel(II)-Catalyzed β-C(sp^3^)–H Thiolation of Ketones. *Org. Lett*. **2024**, *26* (42), 9103–9107. https://doi.org/10.1021/acs.orglett.4c03404

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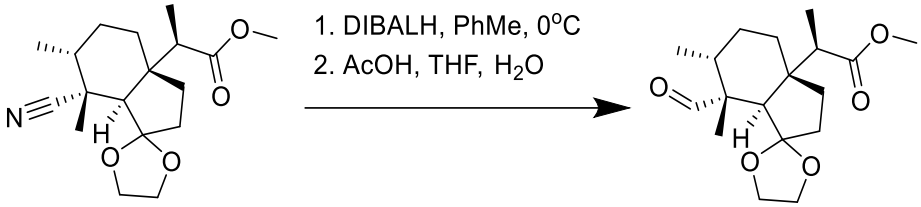

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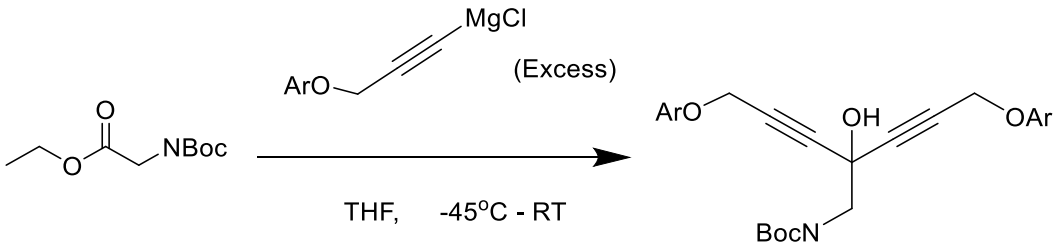
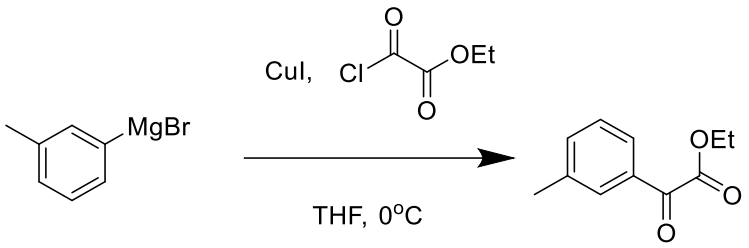
Goethe, O.; DiBello, M.; Herzon, S. B. Total Synthesis of Structurally Diverse Pleuromutilin Antibiotics. *Nat. Chem.* **2022**, *14* (11), 1270-1277. https://doi.org/10.1038/s41557-022-01027-7

10b.2.7



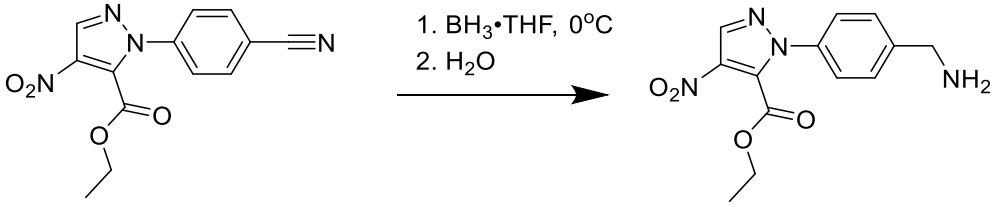
Solas, M.; Renedo, L.; Suárez-Pantiga, S.; Sanz, R. Synthesis of 4-Furan- and 4-Pyrrol-3-yl-2H-chromenes from Naturally-Occurring Compounds by Gold(I)-Catalyzed Domino Reactions. *Adv. Synth. Catal*. 2023, *365*, 2049–2058. https://doi.org/10.1002/adsc.202300307

10b.2.8



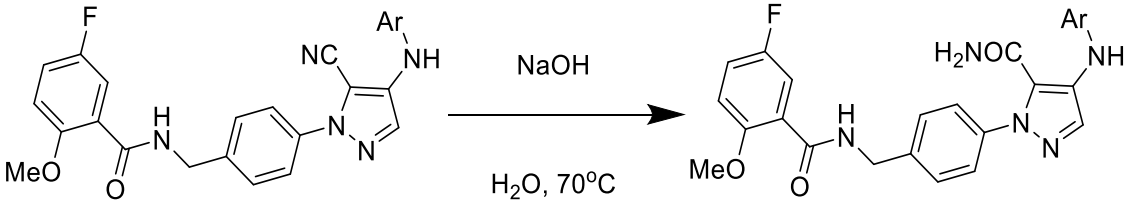
Yang, Y.-C.; Li, W.-S.; Uang, T.-Y.; Kuo, T.-S.; Wu, H.-L. Access to Chiral Tertiary α-Hydroxyesters via Rhodium-Catalyzed Enantioselective Allylation of α-Ketoesters. *Chem. Asian J*. 2026, *21* (2), e70585. https://doi.org/10.1002/asia.70585

10b.2.9



Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* 2026, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

10b.2.10



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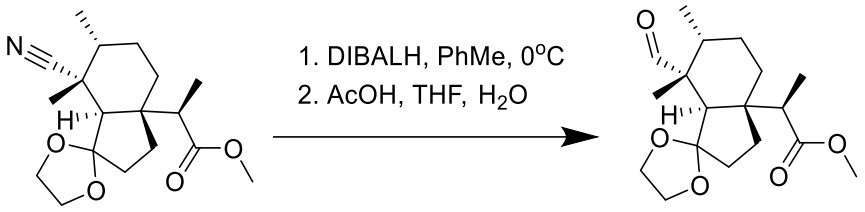
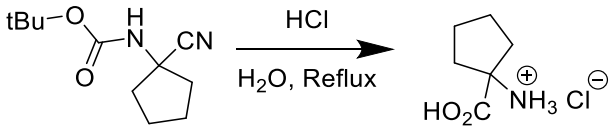
10b.2.11



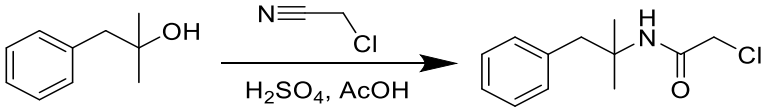
Goethe, O.; DiBello, M.; Herzon, S. B. Total Synthesis of Structurally Diverse Pleuromutilin Antibiotics. *Nat. Chem.* 2022, *14* (11), 1270-1277. https://doi.org/10.1038/s41557-022-01027-7

10b.2.12



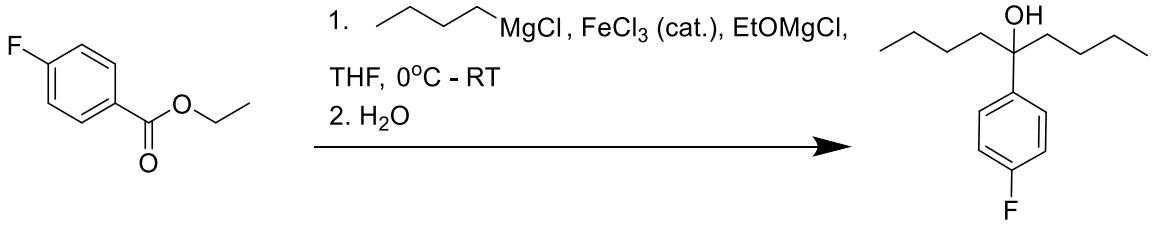
Zhang, Y.-H.; Jiao, F.-N.; Cao, F.-Y.; Zhao, M.-Z.; Sun, B.-Y.; Zhou, M.-J.; Xiao, H.; Dai, J.-J. Practical and Direct Synthesis of α-Aminonitriles Using N-Boc-O-tosyl Alkylhydroxylamines and TMSCN. *Chem. Commun*. 2026, *62* (66), 16531–16535. https://doi.org/10.1039/D6CC03609K

10b.2.13



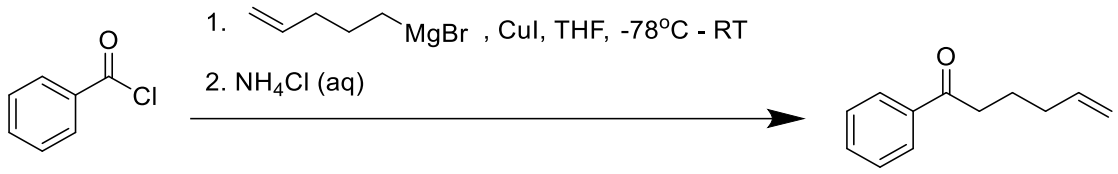
Enudi, O. C.; Twitty, J. C.; Rotella, M. E.; Underwood, S. J.; Kozlowski, M. C.; Watson, M. P. Pyridinium Design for Deaminative Reactions of Sterically Encumbered Alkyl Amines. *Org. Lett*. 2026, *28* (22), 7009–7014. https://doi.org/10.1021/acs.orglett.6c01717

10b.2.14



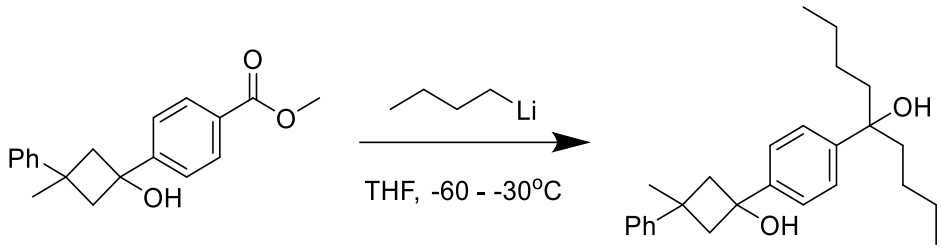
Cahiez, G.; Lefèvre, G.; Moyeux, A.; Guerret, O.; Gayon, E.; Guillonneau, L.; Lefèvre, N.; Gu, Q.; Zhou, E. Gram-Scale, Cheap, and Eco-Friendly Iron-Catalyzed Cross-Coupling between Alkyl Grignard Reagents and Alkenyl or Aryl Halides. *Org. Lett*. 2019, *21* (8), 2679–2683. https://doi.org/10.1021/acs.orglett.9b00665

10b.2.15



Wang, Y.; Hong, F.; Robertson, C. M.; Mudd, R. J.; Bower, J. F. Iridium-Catalyzed Stereoselective α-Alkylation of α-Hydroxy Ketones with Minimally Polarized Alkenes. *J. Am. Chem. Soc*. 2026, *148* (4), 3911–3917. https://doi.org/10.1021/jacs.5c19724

10b.2.16



Note: The authors used butyl lithium instead of a Grignard reagent.

Parra-García, S.; Ballester-Ibáñez, M.; García-López, J.-A. Pd-Catalyzed Formal [2 + 2]-Retrocyclization of Cyclobutanols via 2-Fold Csp^3^−Csp^3^ Bond Cleavage. *J. Org. Chem*. 2024, *89* (2), 882–886. https://doi.org/10.1021/acs.joc.3c01750

Section 11a: Alpha-Carbon Chemistry 1

Required foundation for this section:

Alpha-carbon chemistry

Enol/enolate formation

Aldol addition and condensation

Crossed aldols

Claisen-Schmidt

Halogenation (including Hell-Volhard-Zelinsky reaction)

Claisen condensation

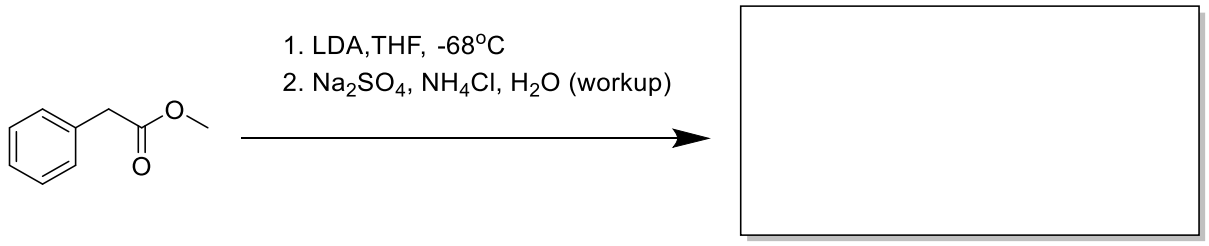
Dieckmann cyclization

Malonic and acetoacetic ester syntheses (alkylation then decarboxylation)

Section 11a – Box-Type Questions

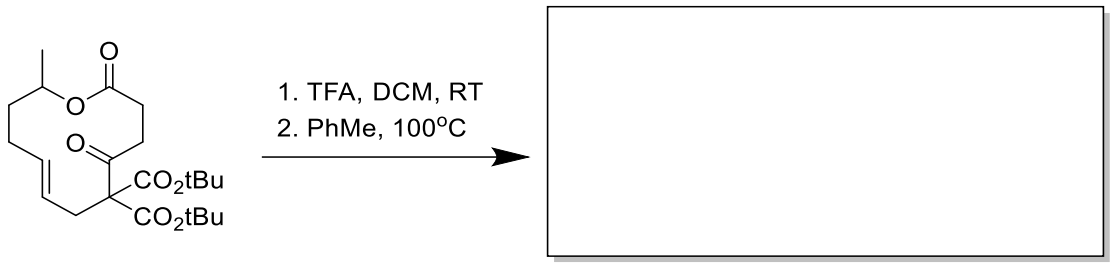
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

11a.1.1



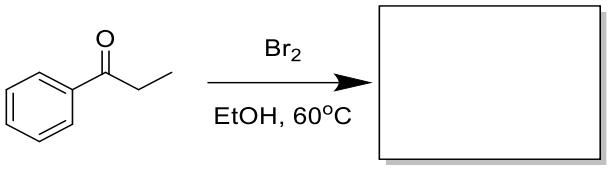
Tang, W.; Guo, L.; Yang, L.; Qiu, L.; Liu, H.; Yang, M. Enhanced Utilization of Ester Enolates in Slow-Kinetic α-Functionalization of Esters: Insights into Enolate Consumption and Preservation Strategies. *Chem. Eng. Sci.* **2026**, *327*, 123675. https://doi.org/10.1016/j.ces.2026.123675

11a.1.2



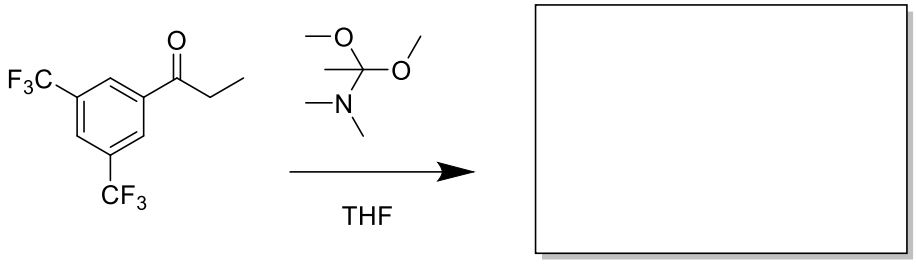
Yang, X.-H.; Jie, T.-C.; Lu, Y.-P.; Chen, S.-Q.; Ran, G.-Y. Combining Palladium and Metal Alkoxide Enables Chemoselective Access to Flexible Allyl-Pd Oxa-dipoles for Higher-Order Cycloadditions. *Org. Lett.* **2026**, *28* (4), 1247-1252. https://doi.org/10.1021/acs.orglett.5c05011

11a.1.3



Özkan, G.; Biçer, A.; Bulca, Z. T.; Kurt, E.; Akbulut, D.; Köse, F. A. Synthesis, Structural Characterization, and Structure-Activity Relationship of Thiazole Derivatives: A Combined Experimental and Computational Study. *J. Mol. Struct.* **2026**, *1374*, 146832. https://doi.org/10.1016/j.molstruc.2026.146832

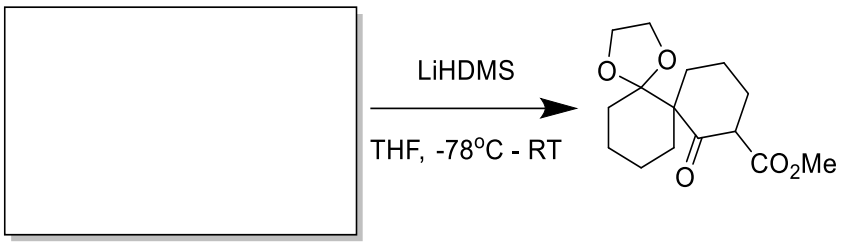
11a.1.4



Note: Assume there is some acid present in the reaction.

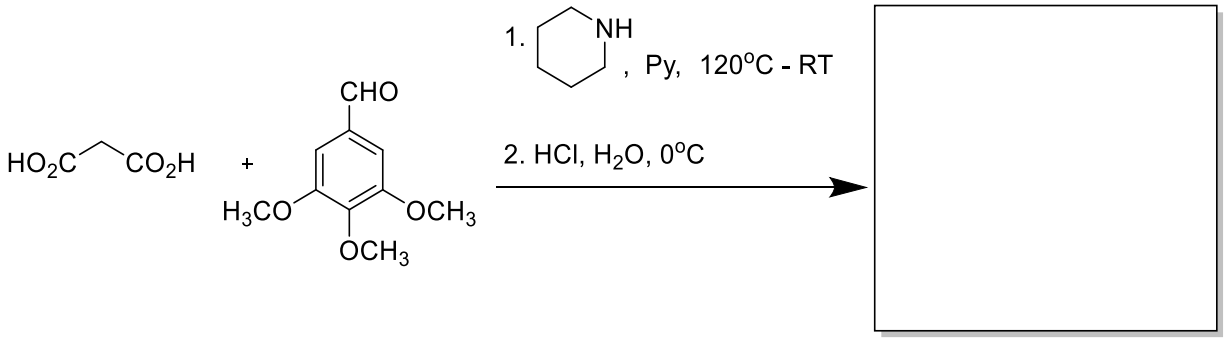
Miao, H.; Qin, Y.; Shao, D.; Chen, Q.; Pan, Y.; Lei, M.; Wu, R.; Ye, X.; Wang, X.; Zhu, Y. Discovery of SZJK-0421: A Novel Potent, Low Toxicity, Selective Second Generation of CRM1 Inhibitor for the Treatment of Both Hematological and Solid Tumors. *J. Med. Chem.* **2024**, *67* (22), 20595–20618. https://doi.org/10.1021/acs.jmedchem.4c02169

11a.1.5



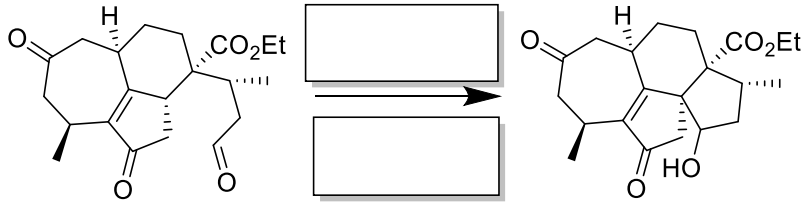
Broeker, J.; Waterson, A. G.; Hodges, T. R.; Abbott, J. R.; Arnold, A.; Böttcher, J.; Braun, N.; Cui, J.; Fuchs, J. E.; Gerstberger, T.; Gogg, S.; Hanner, S.; Herdeis, L.; Howell, L. W.; Mantoulidis, A.; Mayer, M.; Phan, J.; Rocchetti, F.; Sankar, K. Discovery of BI-2493, a Pan-KRAS Inhibitor Showing In Vivo Efficacy. *J. Med. Chem.* **2025**, *68* (15), 15649-15668. https://doi.org/10.1021/acs.jmedchem.5c00576

11a.1.6



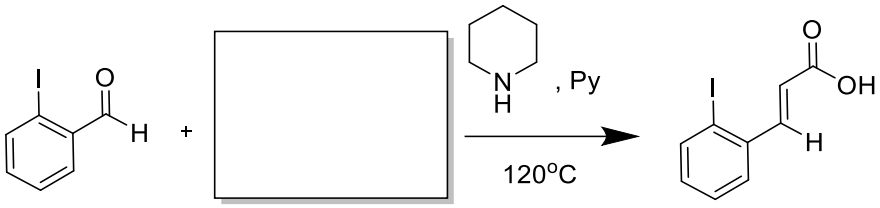
Shi, S.; Tu, J.; Zhong, M.; Xi, J.; Hao, J.; Wu, Z.; Zhang, H.; Bai, Z.; Zhang, B. Structure-Guided Optimization of PAO-PDT Yields TrxR Inhibitors as Potential Anticancer Agent. *Eur. J. Med. Chem.* **2026**, *303*, 118407. https://doi.org/10.1016/j.ejmech.2025.118407

11a.1.7



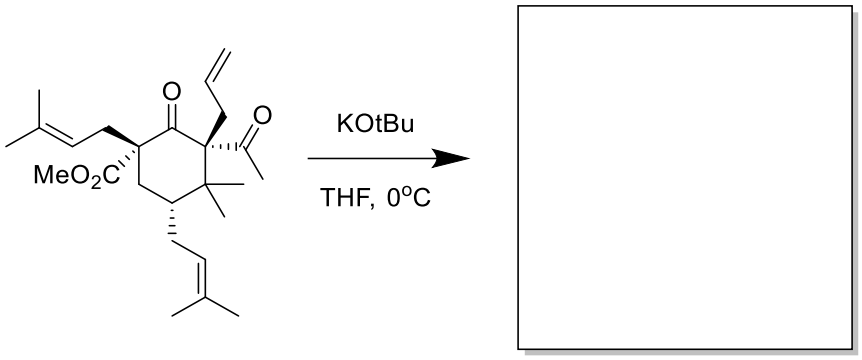
Mao, H.-K.; Wang, Q.; Xu, J. Enantioselective Total Synthesis of Fortalpinoid Q via a $TEMPO^{+}$ BF_4^{-} -Mediated Dehydrative Nazarov Cyclization. *J. Am. Chem. Soc.* **2025**, *147* (11), 9079–9084. https://doi.org/10.1021/jacs.5c00319

11a.1.8



Liu, S.; Díaz-Fernández, M.; Zhang, M.; Huang, F.; Chen, Y.; Yang, Y.; Marín-Beloqui, J. M.; Lan, J.; You, J.; Casado, J.; Zhang, C. Azuperylene: The Nonalternant Isomer of Perylene. *Angew. Chem. Int. Ed.* **2025**, *64* (29), e202505897. https://doi.org/10.1002/anie.202505897

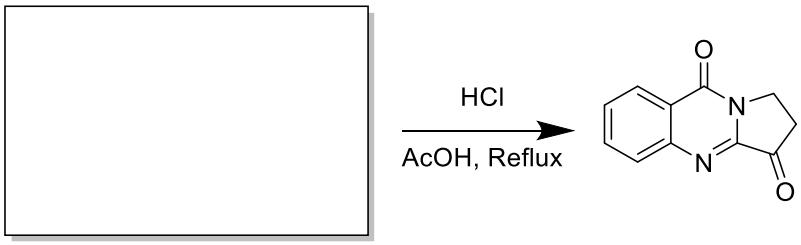
11a.1.9



Hint: A new ring is formed in the product.

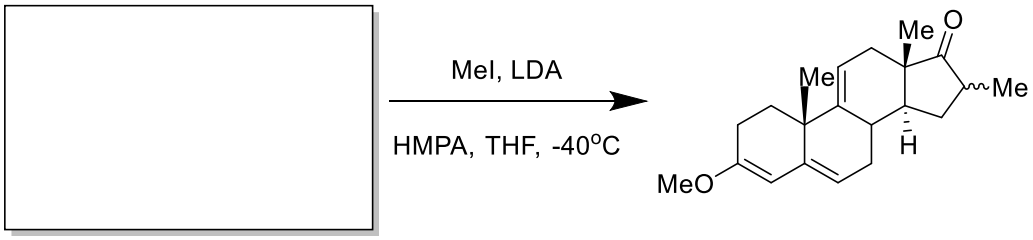
Wan, Y.; Wu, H.; Xia, L.; Liu, S.; Ren, Y.; Xu, H.; Zheng, C. Sequential Dieckmann Cyclization Enables the Total Synthesis of 7- *Epi* -Clusianone and 18-Hydroxy-7- *Epi* -Clusianone. *Org. Biomol. Chem.* **2024**, *22* (3), 529–537. https://doi.org/10.1039/D3OB01840G

11a.1.10



D'Almeida, R. E.; Chen, P.; Huang, Y.; Goetz, E.; Sammeta, V. R.; Yang, B.; Rao, R. P.; Rasapalli, S.; Elfawal, M. A. Design, Synthesis, and Biological Evaluation of a Focused Pyrrolo- and Pyrido-Quinazolinone Natural Products-Templated Library for Anti-Fungal and Anthelmintic Activities. *Bioorg. Med. Chem.* **2026**, *134*, 118517. https://doi.org/10.1016/j.bmc.2025.118517

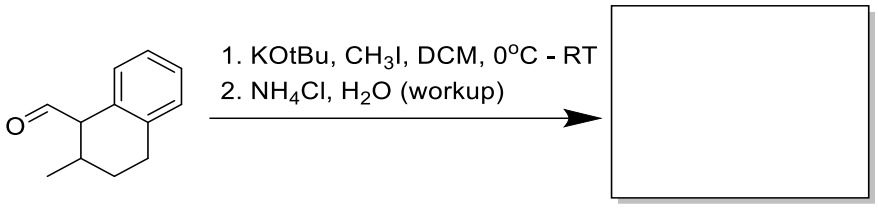
11a.1.11



Assume there is only one equivalent of MeI added.

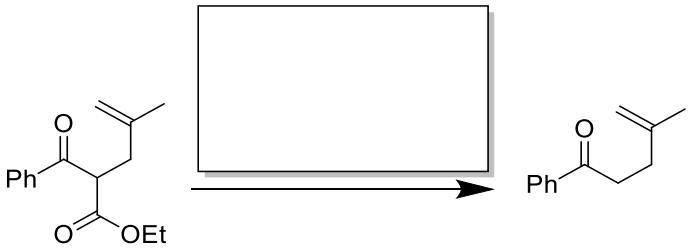
Wei, J.; Zhang, Y.; Liu, M.; Ning, Y.; Cao, Y.; Chen, F.-E. Divergent Chemo- and Biocatalytic Route to 16β-Methylcorticoids: Asymmetric Synthesis of Betamethasone Dipropionate, Clobetasol Propionate, and Beclomethasone Dipropionate. *Angew. Chem. Int. Ed.* **2024**, *63* (4), e202313952. https://doi.org/10.1002/anie.202313952

11a.1.12



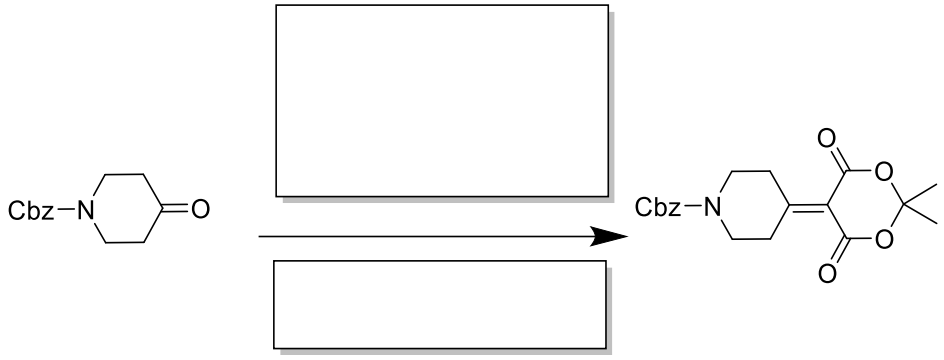
Kong, L.; Gan, X.-C.; van der Puyl Lovett, V. A.; Shenvi, R. A. Alkene Hydrobenzylation by a Single Catalyst That Mediates Iterative Outer-Sphere Steps. *J. Am. Chem. Soc.* **2024**, *146* (4), 2351-2357. https://doi.org/10.1021/jacs.3c13398

11a.1.13



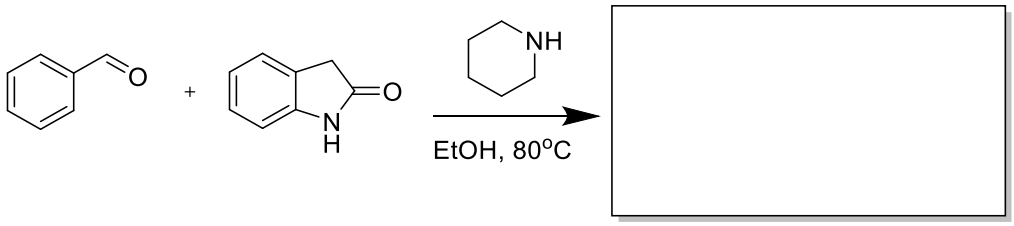
Chen, T.; Li, J.; Hu, X.; Li, J.; Wang, Z.; Yan, Z.; Xu, Z.-F.; Yu, M.; Li, C.-Y. Oxidative Cleavage of Olefins via *N*-Arylaminophthalimide-Derived Aryl Radicals under Air. *Org. Lett.* **2026**, *28* (18), 5734-5739. https://doi.org/10.1021/acs.orglett.6c01182

11a.1.14



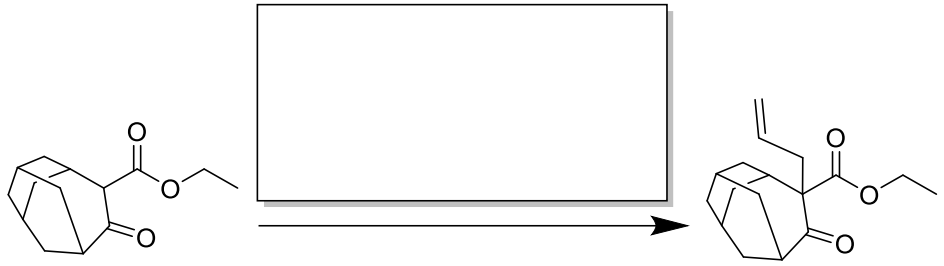
Chu, G.-H.; Le Bourdonnec, B.; Gu, M.; Saeui, C. T.; Dolle, R. E. General and Efficient Synthetic Approach to Novel Tricyclic Spiroketones. *Tetrahedron* **2009**, *65* (27), 5161-5167. https://doi.org/10.1016/j.tet.2009.04.094

11a.1.15



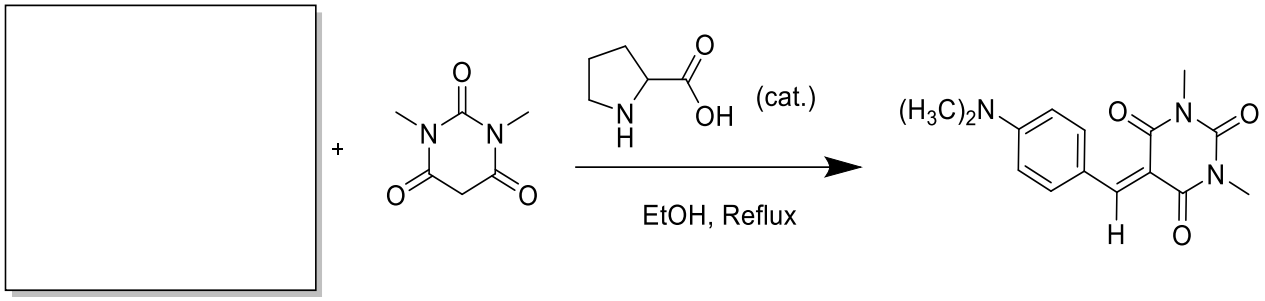
Banyangala, M.; K. S., S.; Thushara, R.; C. S., A.; K., L. V.; Suresh, C. H.; Purushothaman, J.; Somappa, S. B. Regioselective House-Meinwald Rearrangement in Oxindoles: Access to Substituted Quinolinones. *Org. Biomol. Chem.* **2026**, *24* (10), 2028-2033. https://doi.org/10.1039/D6OB00128A

11a.1.16



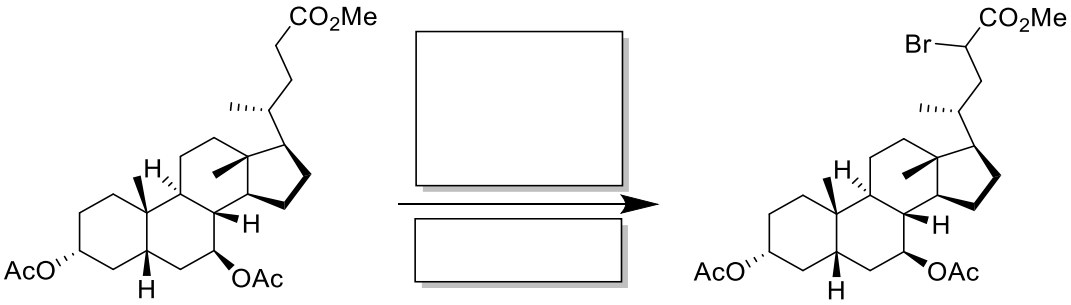
Tkachenko, I. M.; Mankova, P. A.; Rybakov, V. B.; Golovin, E. V.; Klimochkin, Y. N. Wagner–Meerwein Type Rearrangement in 5-Oxohomoadamantane Series. *Org. Biomol. Chem.* **2020**, *18* (3), 465–478. https://doi.org/10.1039/C9OB02060H.

11a.1.17



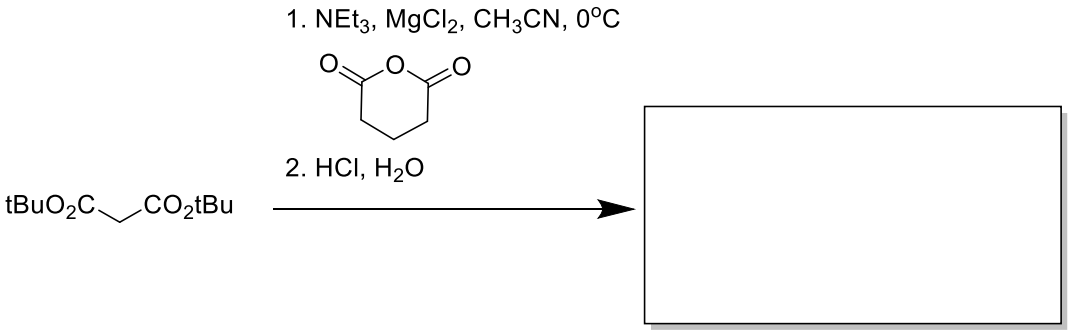
Li, P.; Zhang, J.; Wang, Z.; Li, C.; Wu, H.; Lei, M.; Yan, G.; Tian, H.; Gu, R.; Qu, D.-H. Catalyst-Free Dynamic Covalent Knoevenagel/Hydrazide Condensation for Polyacylhydrazones and Covalent Adaptable Networks. *Angew. Chem. Int. Ed.* **2025**, *64* (29), e202506939. https://doi.org/10.1002/anie.202506939

11a.1.18



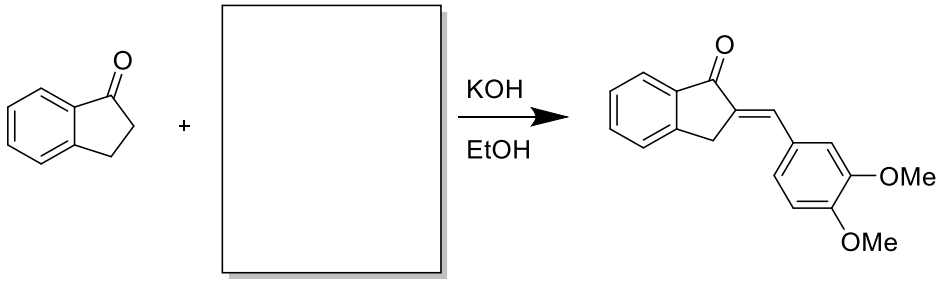
Yang, R.; Du, C.; Cao, T.; Wang, G.; Jiang, X.; Gao, J.; Lin, T.; Sun, C.; Ding, R.; Tian, W.; Chen, H. Synthesis and Anti-Hepatoma Activities of U12 Derivatives Arresting G0/G1 Phase and Inducing Apoptosis by PI3K/AKT/mTOR Pathway. *Pharmaceuticals* **2022**, *15* (1), 107. https://doi.org/10.3390/ph15010107

11a.1.19



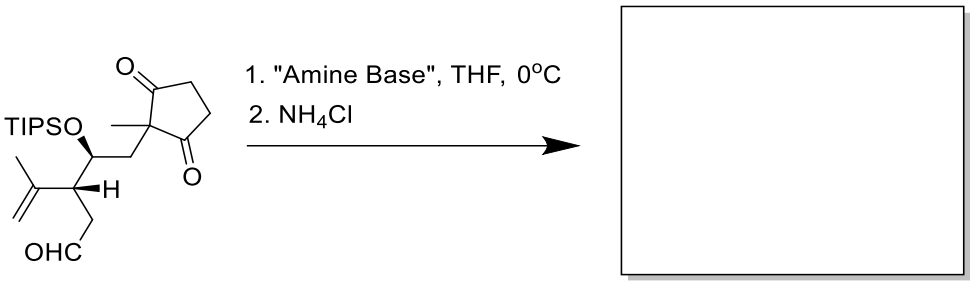
Yang, X.-H.; Jie, T.-C.; Lu, Y.-P.; Chen, S.-Q.; Ran, G.-Y. Combining Palladium and Metal Alkoxide Enables Chemoselective Access to Flexible Allyl-Pd Oxa-Dipoles for Higher-Order Cycloadditions. *Org. Lett.* **2026**, *28* (4), 1247–1252. https://doi.org/10.1021/acs.orglett.5c05011

11a.1.20



Story, J. B.; Ringler, K. E.; Nguyen, C. L.; Drance, M. J.; Howard, E. M. Synthesis of 2-Naphthols via a Trifluoroacetic Acid-Mediated Epoxy Alcohol Rearrangement. *J. Org. Chem.* **2026**, *91* (14), 5249–5254. https://doi.org/10.1021/acs.joc.6c00021

11a.1.21



Note: The article employs a specialized amine base to facilitate the transformation and achieve the desired stereochemical outcome.

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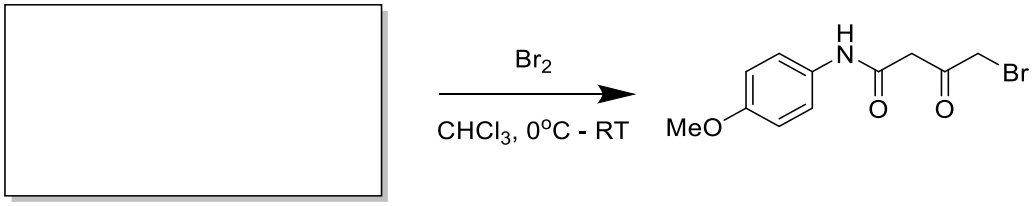

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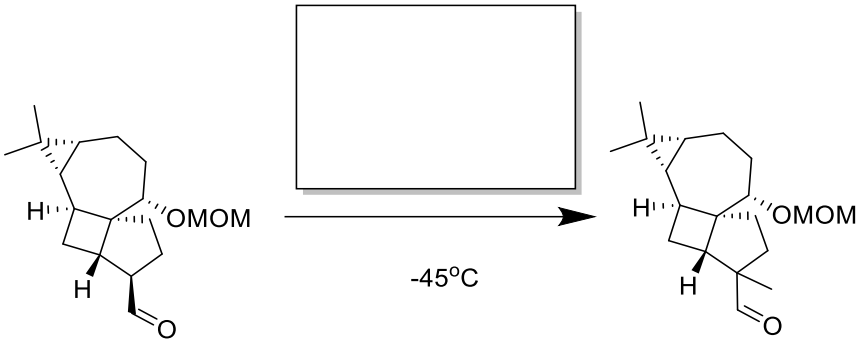

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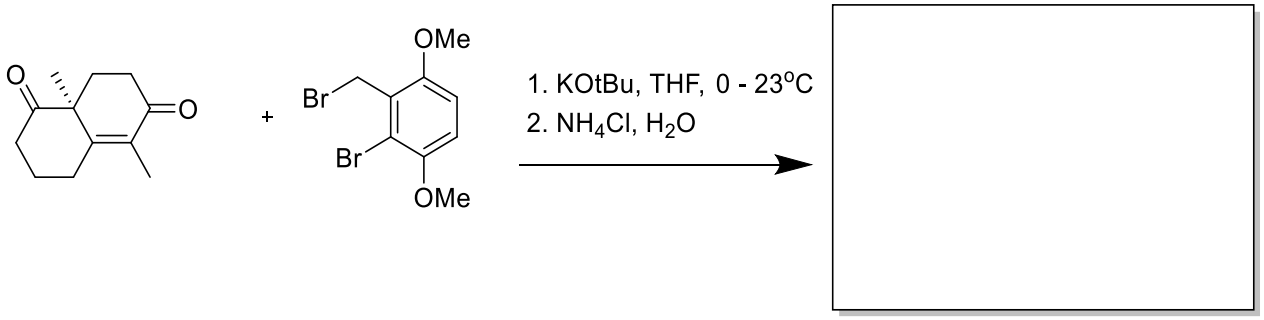

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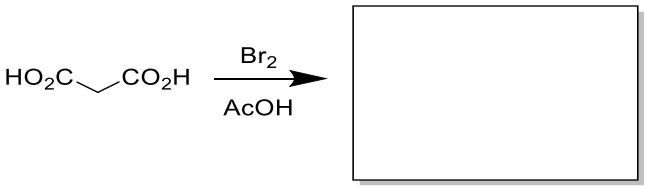

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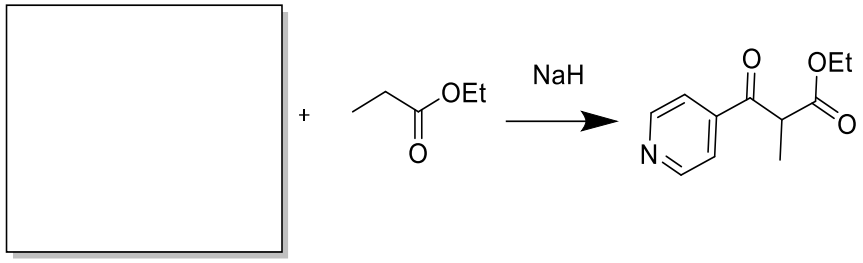

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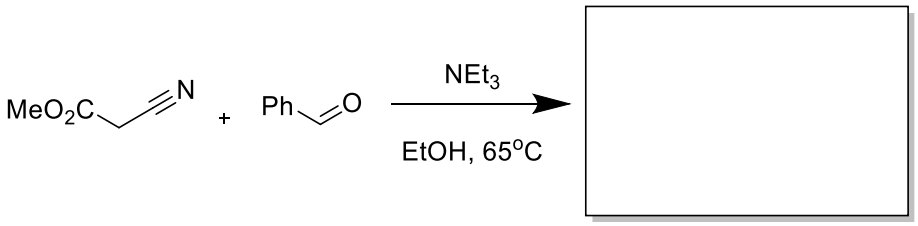

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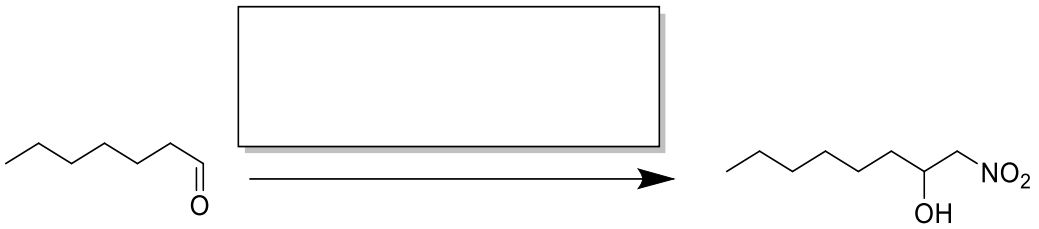

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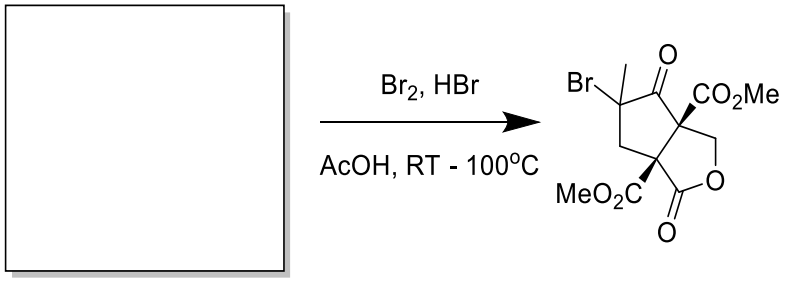

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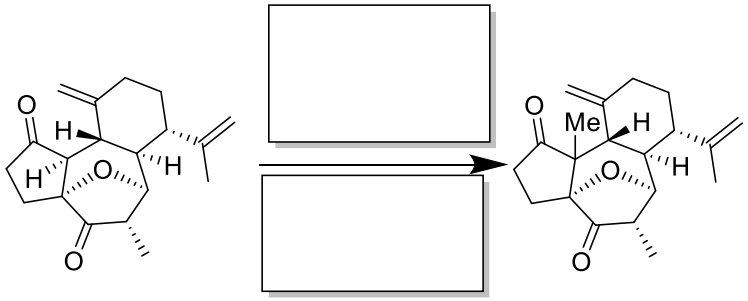

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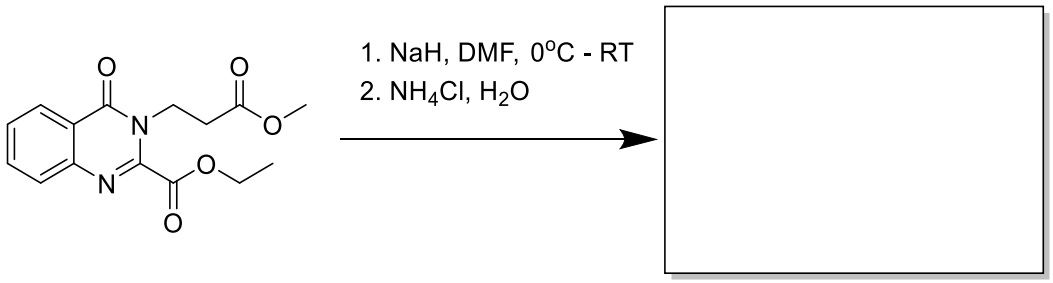

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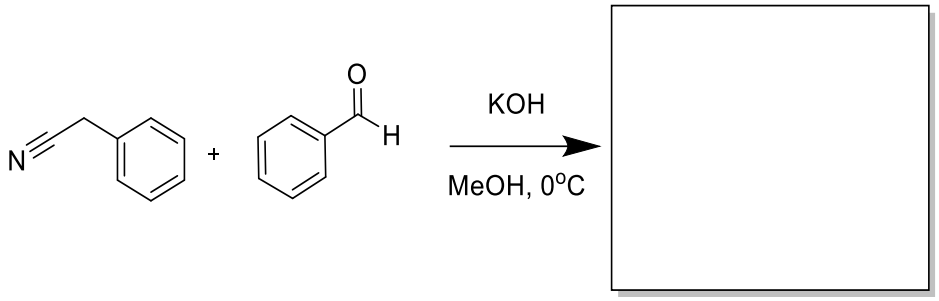

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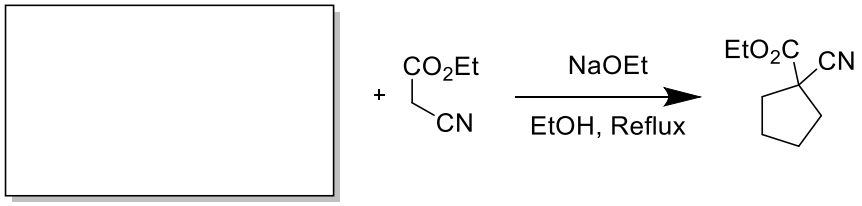

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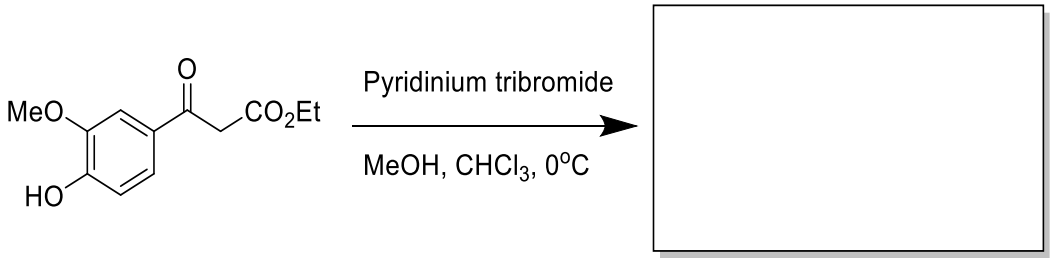

Note: Pyridinium tribromide is a source for molecular bromine.

Bourmaud, C. L.; Bertella, S.; Bosch Rico, A.; Karlen, S. D.; Ralph, J.; Luterbacher, J. S. Quantification of Native Lignin Structural Features with Gel-Phase 2D-HSQC$_0$ Reveals Lignin Structural Changes During Extraction. *Angew. Chem. Int. Ed.* **2024**, *63* (31), e202404442. https://doi.org/10.1002/anie.202404442

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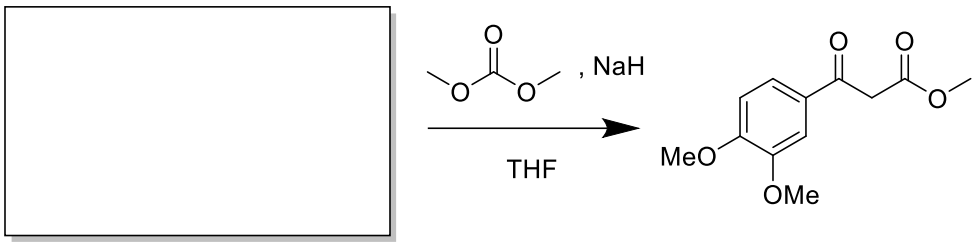

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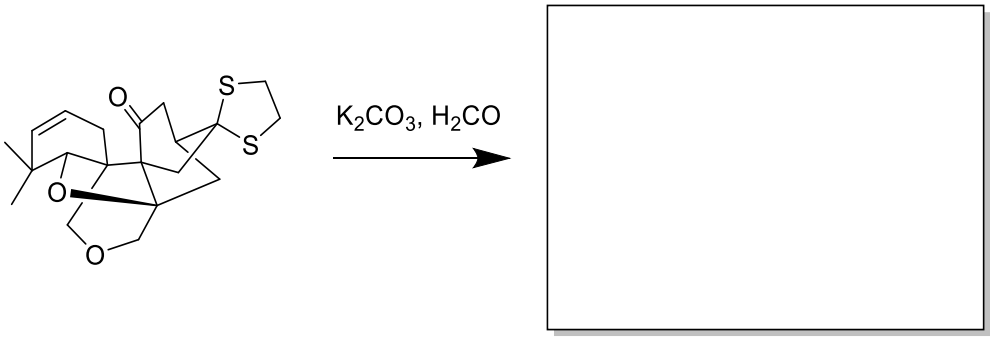

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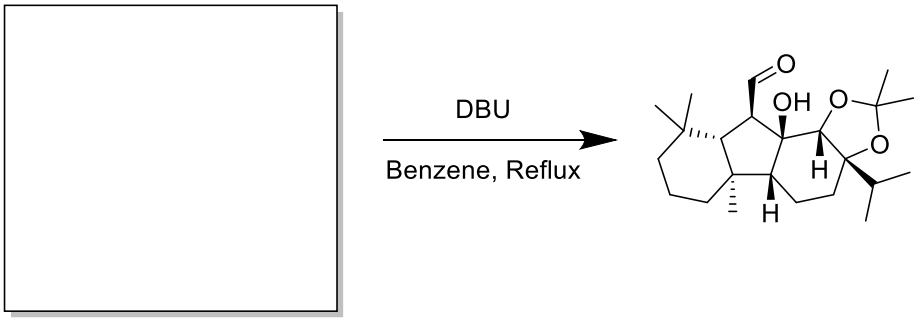

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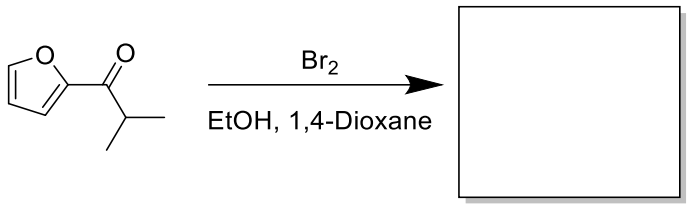

Seleznev, Y. A.; Lavrinchenko, I. A.; Moseev, T. D.; Varaksin, M. V.; Tsmokaluk, A. N.; Mazhukin, D. G.; Tikhonov, A. Y.; Charushin, V. N.; Chupakhin, O. C(2) and C(5) Nucleophilic Functionalization of 4 *H* -Imidazole-3-Oxide Exposed to Carboranyllithium. *J. Org. Chem.* **2025**, *90* (50), 17688–17704. https://doi.org/10.1021/acs.joc.5c01956

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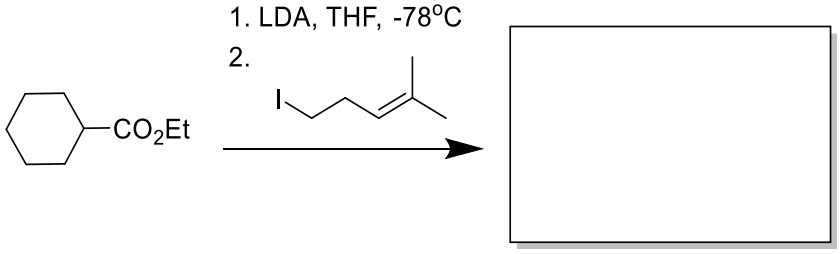

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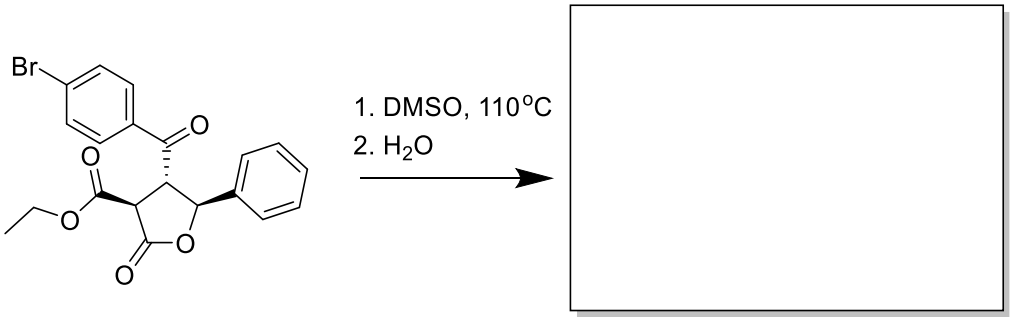

Deerkadharshini, M.; Ezhilgnanadevi, E.; Srinivasan, K. Stereoselective Synthesis of 2-(β-Aroylstyryl)malonates and γ-Butyrolactones through Lewis Acid-Mediated Ring-Opening Reactions of Aroyl-Substituted Donor-Acceptor Cyclopropanes. *J. Org. Chem.* **2026**, *91* (27), 9243-9251. https://doi.org/10.1021/acs.joc.6c00070

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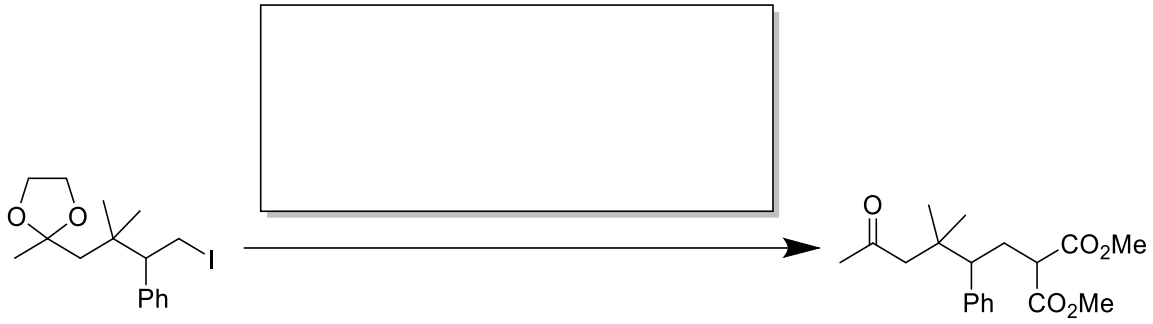
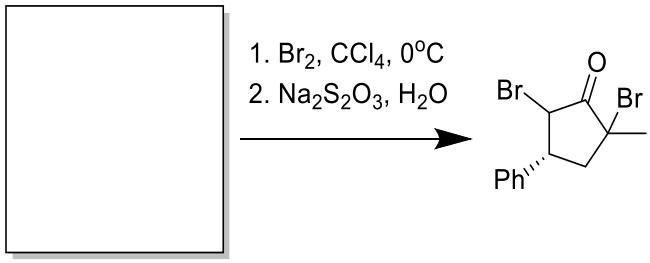


Wan, Y.; Wu, H.; Xia, L.; Liu, S.; Ren, Y.; Xu, H.; Zheng, C. Sequential Dieckmann Cyclization Enables the Total Synthesis of 7- *Epi* -Clusianone and 18-Hydroxy-7- *Epi* -Clusianone. *Org. Biomol. Chem.* **2024**, *22* (3), 529–537. https://doi.org/10.1039/D3OB01840G

11a.1.42



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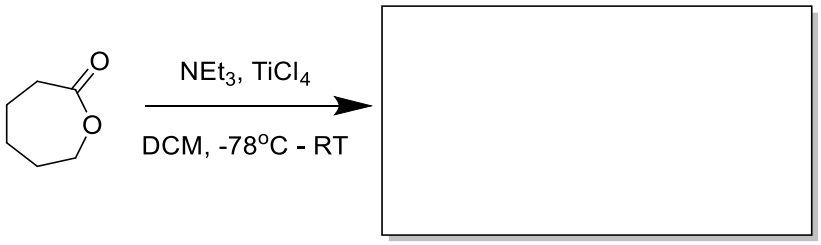
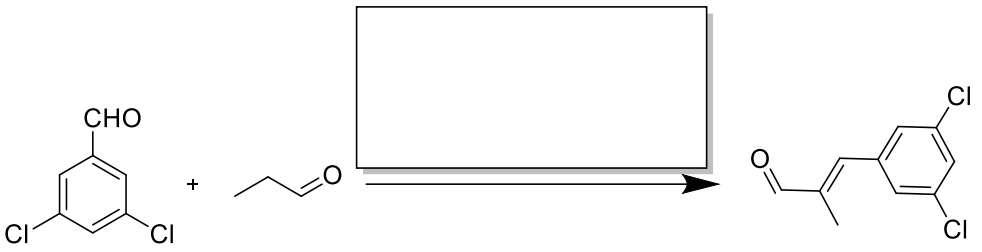
11a.1.43



Note: $TiCl_4$ is a Lewis Acid used to make a carbonyl group more reactive to nucleophilic attack.

Nabi, A.; Atmuri, N. D. P.; Arnold, D.; Saadati, F.; Tran, H.; Adak, T.; Dake, G. R.; Ciufolini, M. A. Claisen Self-Condensation of Lactones in the Synthesis of Ionizable Lipids. *J. Org. Chem.* **2024**, *89* (17), 12775–12778. https://doi.org/10.1021/acs.joc.4c01193

11a.1.44



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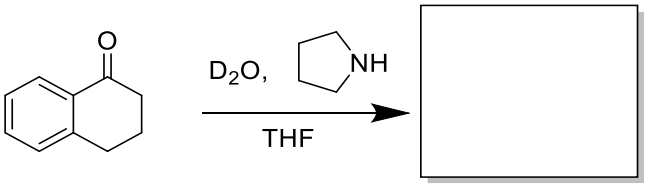

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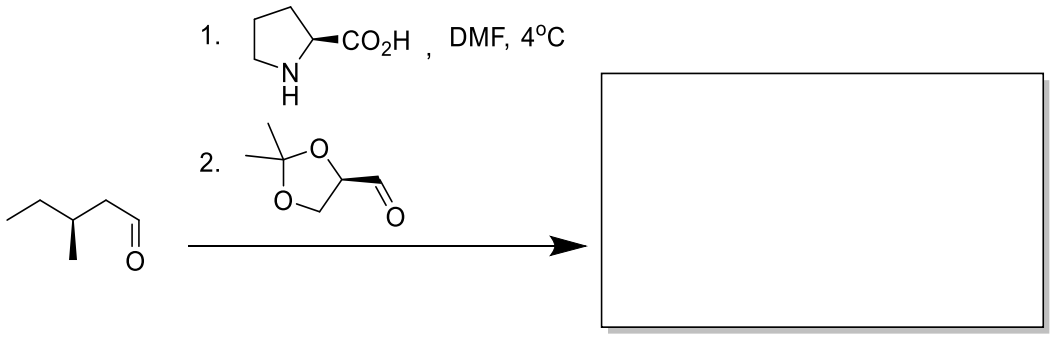

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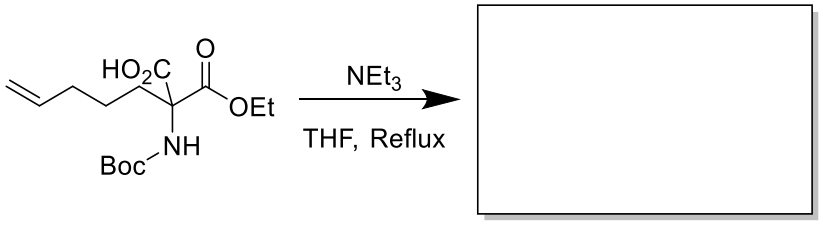
11a.1.47



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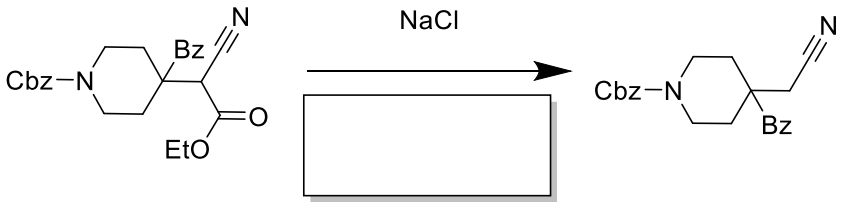

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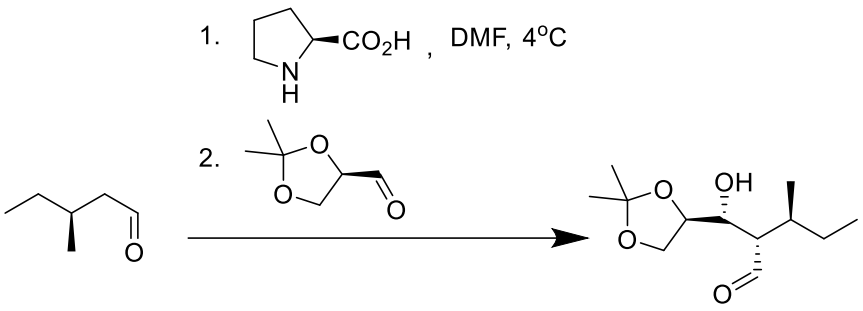
Section 11a – Mechanism Questions

Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

11a.2.1



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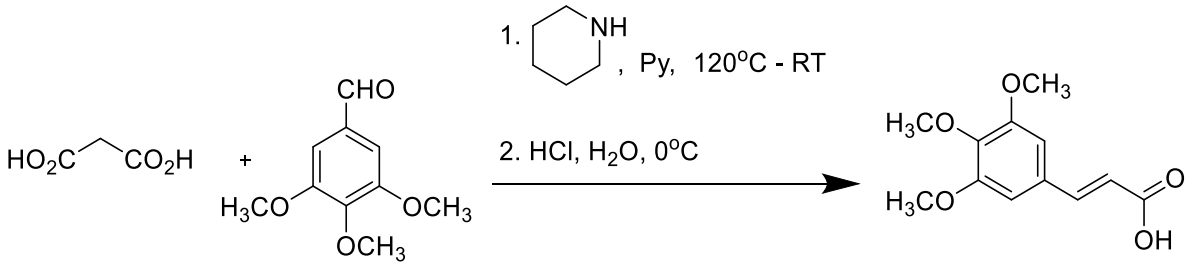
11a.2.2



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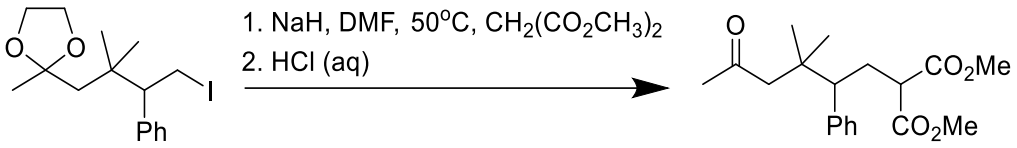
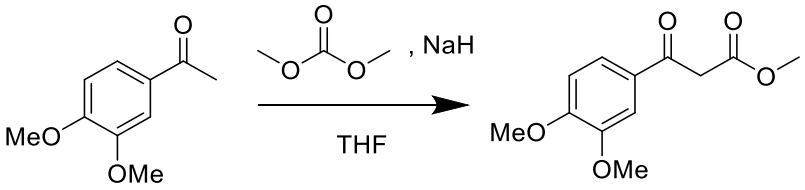
11a.2.3



Wan, Y.; Wu, H.; Xia, L.; Liu, S.; Ren, Y.; Xu, H.; Zheng, C. Sequential Dieckmann Cyclization Enables the Total Synthesis of 7- *Epi* -Clusianone and 18-Hydroxy-7- *Epi* -Clusianone. *Org. Biomol. Chem.* **2024**, *22* (3), 529–537. https://doi.org/10.1039/D3OB01840G

11a.2.4



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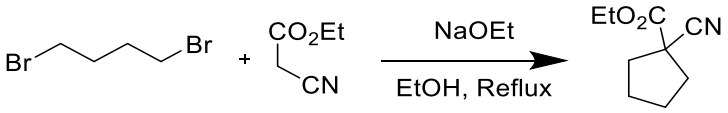

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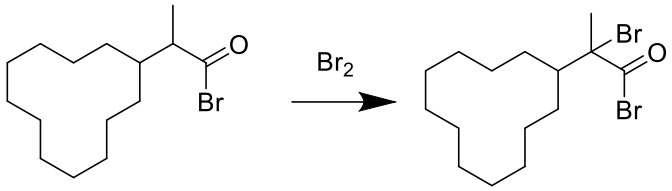
11a.2.6



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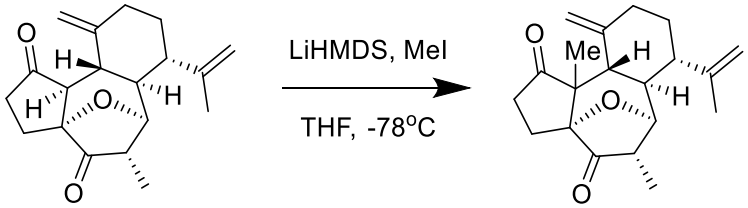
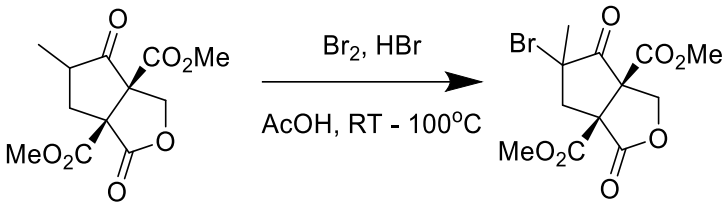
11a.2.7



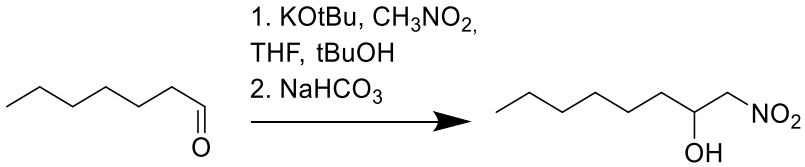
Peng, Y.-C.; Lin, D.-Y.; Deng, X.; Zhang, W.; Zhou, F.; Ke, X.; Li, C.-C. Total Synthesis and Structural Confirmation of Curcusone I. *J. Am. Chem. Soc.* **2026**, *148* (32), 34088-34093. https://doi.org/10.1021/jacs.6c13015

11a.2.8



Wright, A. I.; Zhang, C.; Cao, J.; Nakano, Y.; Sánchez-Jiménez, L.; DeBono, J.; Kapatkar, S.; Challis, G. L.; Lupton, D. W. Phosphine-Mediated (3 + 2) Cycloaddition of Electron-Poor Terminal Alkynes: A Concise Route to Premethylenomycin C Lactone. *J. Org. Chem.* **2025**, *90* (31), 11230–11236. https://doi.org/10.1021/acs.joc.5c01179

11a.2.9



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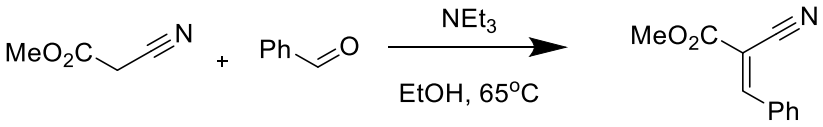
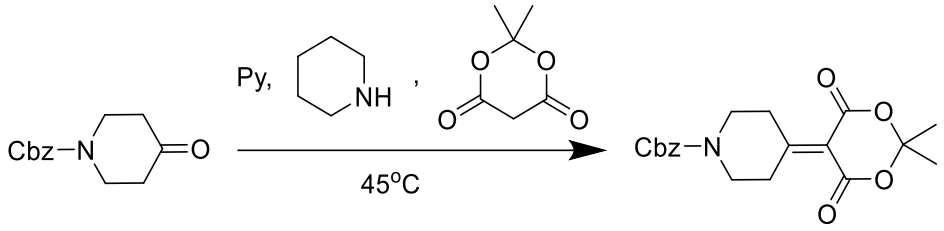
11a.2.10



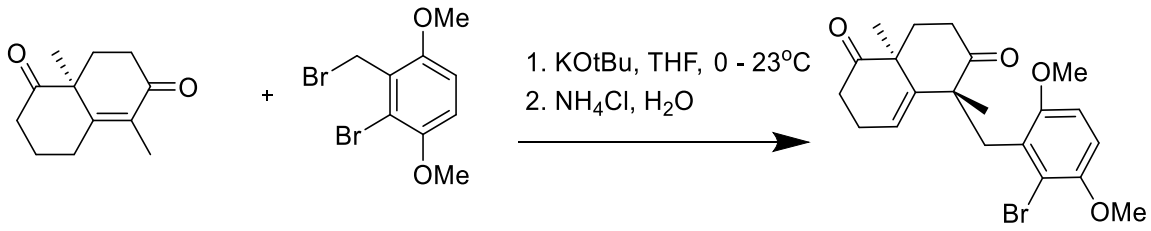
Narayanan, D.; Tran, K. T.; Pallesen, J. S.; Solbak, S. M. Ø.; Qin, Y.; Mukminova, E.; Luchini, M.; Vasilyeva, K. O.; González Chichón, D.; Goutsiou, G.; Poulsen, C.; Haapanen, N.; Popowicz, G. M.; Sattler, M.; Olagnier, D.; Gajhede, M.; Bach, A. Development of Noncovalent Small-Molecule Keap1-Nrf2 Inhibitors by Fragment-Based Drug Discovery. *J. Med. Chem.* **2022**, *65* (21), 14481–14526. https://doi.org/10.1021/acs.jmedchem.2c00830

11a.2.11



Chu, G.-H.; Le Bourdonnec, B.; Gu, M.; Saeui, C. T.; Dolle, R. E. General and Efficient Synthetic Approach to Novel Tricyclic Spiroketones. *Tetrahedron* **2009**, *65* (27), 5161-5167. https://doi.org/10.1016/j.tet.2009.04.094

11a.2.12



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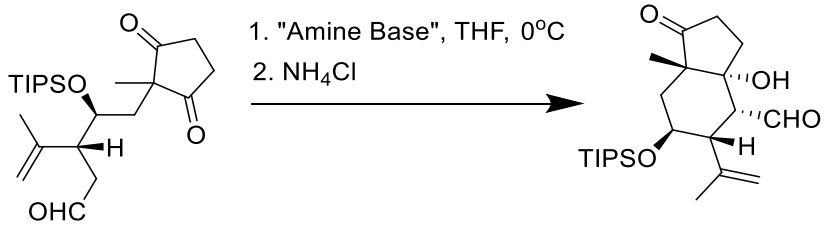
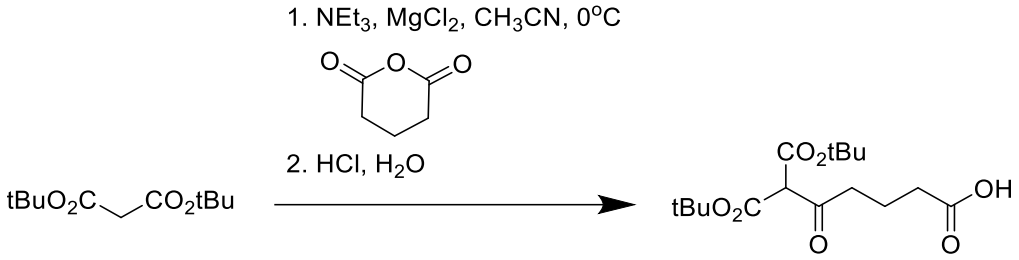
11a.2.13



Note: The article employs a specialized amine base to facilitate the transformation and achieve the desired stereochemical outcome. For the reaction mechanism, use "$:NR_3$".

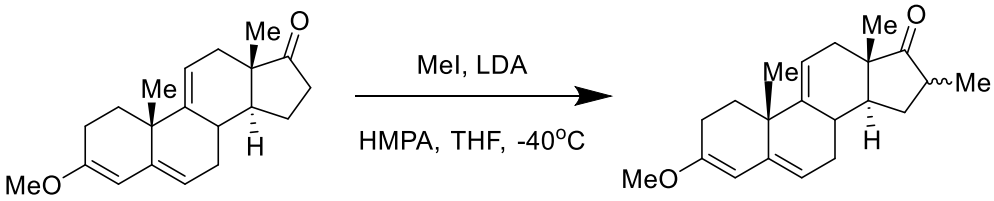
Ikeuchi, K.; Haraguchi, S.; Fujii, R.; Yamada, H.; Suzuki, T.; Tanino, K. Total Synthesis of (+)-Coriamyrtin via a Desymmetrizing Strategy Involving a 1,3-Cyclopentanedione Moiety. *Org. Lett.* **2023**, *25* (16), 2751–2755. https://doi.org/10.1021/acs.orglett.3c00249

11a.2.14



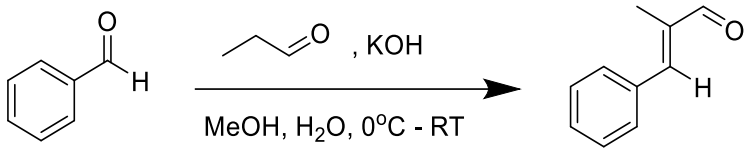
Yang, X.-H.; Jie, T.-C.; Lu, Y.-P.; Chen, S.-Q.; Ran, G.-Y. Combining Palladium and Metal Alkoxide Enables Chemoselective Access to Flexible Allyl-Pd Oxa-Dipoles for Higher-Order Cycloadditions. *Org. Lett.* **2026**, *28* (4), 1247–1252. https://doi.org/10.1021/acs.orglett.5c05011

11a.2.15



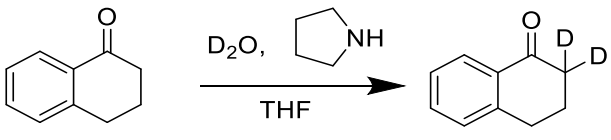
Wei, J.; Zhang, Y.; Liu, M.; Ning, Y.; Cao, Y.; Chen, F.-E. Divergent Chemo- and Biocatalytic Route to 16β-Methylcorticoids: Asymmetric Synthesis of Betamethasone Dipropionate, Clobetasol Propionate, and Beclomethasone Dipropionate. *Angew. Chem. Int. Ed.* **2024**, *63* (4), e202313952. https://doi.org/10.1002/anie.202313952

11a.2.16



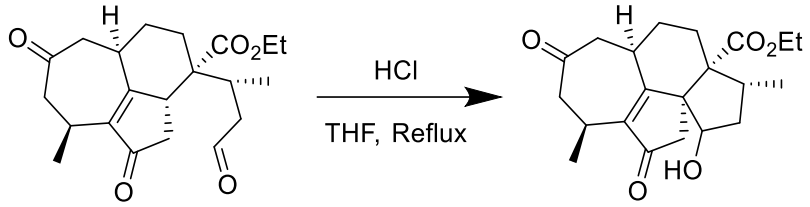
Zeng, Q.-Y.; Zhang, Y.-Q.; Cheng, X.-Y.; Xu, H.; Dai, H.-X. Synthesis of Polysubstituted Pyrroles via (2 + 2 + 1) Cyclization of Enone Oxime Ethers with Alkynes and Diaziridinone. *J. Org. Chem.* **2026**, *91* (3), 1271–1275. https://doi.org/10.1021/acs.joc.5c01879

11a.2.17



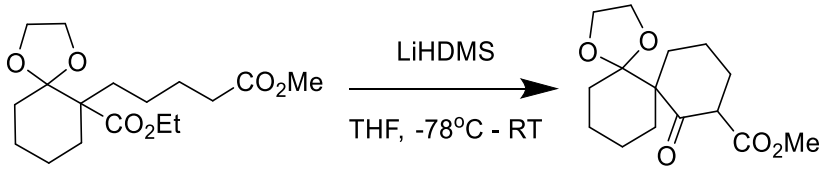
Ikonnikova, V. A.; Solyev, P. N.; Al Mufti, A. M.; Kungurtsev, K. D.; Korlyukov, A. A.; Baranov, M. S.; Mikhaylov, A. A. Synthesis of Chroman Derivatives by Group Transposition and Atom Swapping in 1-Tetralones: Single-Atom Editing Enabled by Oxidative Ring Contraction of Benzoxepine Silyl Ketene Acetals. *Angew. Chem. Int. Ed.* **2025**, *64* (31), e202506564. https://doi.org/10.1002/anie.202506564

11a.2.18



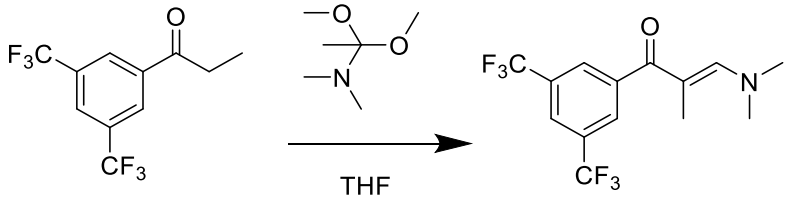
Mao, H.-K.; Wang, Q.; Xu, J. Enantioselective Total Synthesis of Fortalpinoid Q via a TEMPO^{+} BF_4^{-} -Mediated Dehydrative Nazarov Cyclization. *J. Am. Chem. Soc.* **2025**, *147* (11), 9079–9084. https://doi.org/10.1021/jacs.5c00319

11a.2.19



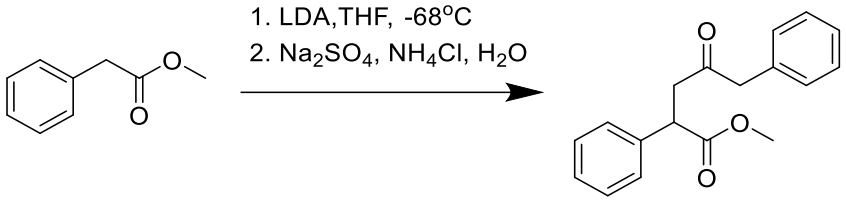
Broeker, J.; Waterson, A. G.; Hodges, T. R.; Abbott, J. R.; Arnold, A.; Böttcher, J.; Braun, N.; Cui, J.; Fuchs, J. E.; Gerstberger, T.; Gogg, S.; Hanner, S.; Herdeis, L.; Howell, L. W.; Mantoulidis, A.; Mayer, M.; Phan, J.; Rocchetti, F.; Sankar, K. Discovery of BI-2493, a Pan-KRAS Inhibitor Showing In Vivo Efficacy. *J. Med. Chem.* **2025**, *68* (15), 15649-15668. https://doi.org/10.1021/acs.jmedchem.5c00576

11a.2.20



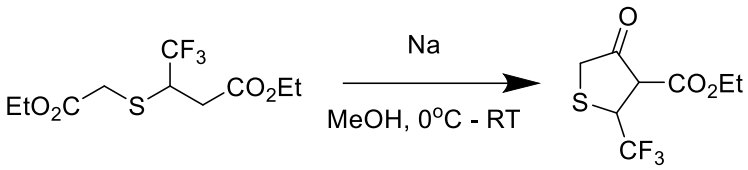
Miao, H.; Qin, Y.; Shao, D.; Chen, Q.; Pan, Y.; Lei, M.; Wu, R.; Ye, X.; Wang, X.; Zhu, Y. Discovery of SZJK-0421: A Novel Potent, Low Toxicity, Selective Second Generation of CRM1 Inhibitor for the Treatment of Both Hematological and Solid Tumors. *J. Med. Chem.* **2024**, *67* (22), 20595–20618. https://doi.org/10.1021/acs.jmedchem.4c02169

11a.2.21



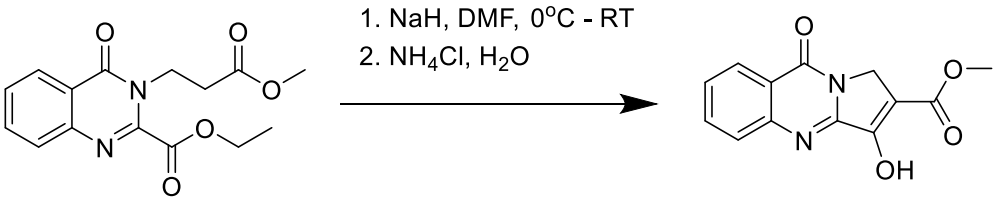
Tang, W.; Guo, L.; Yang, L.; Qiu, L.; Liu, H.; Yang, M. Enhanced Utilization of Ester Enolates in Slow-Kinetic α-Functionalization of Esters: Insights into Enolate Consumption and Preservation Strategies. *Chem. Eng. Sci.* **2026**, *327*, 123675. https://doi.org/10.1016/j.ces.2026.123675

11a.2.22



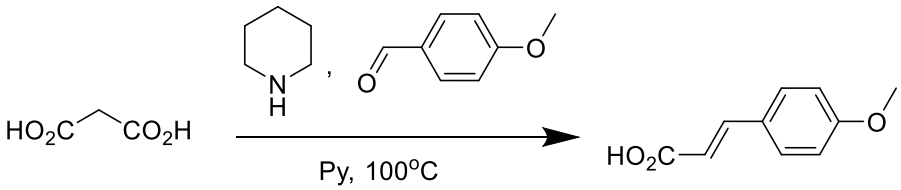
Redka, M. O.; Dovhaniuk, N.; Blahun, O.; Liashuk, O. S.; Hurieva, A. M.; Lesyk, D.; Skrypnik, D.; Holota, Y.; Durylin, D.; Borysko, P.; Kondratov, I. S.; Grygorenko, O. O. Synthesis and Physicochemical Characterization of 5-Trifluoromethyl-Substituted Tetrahydrofurans and Tetrahydrothiophenes. *Eur. J. Org. Chem.* **2026**, *29* (3), e202501086. https://doi.org/10.1002/ejoc.202501086

11a.2.23



D'Almeida, R. E.; Chen, P.; Huang, Y.; Goetz, E.; Sammeta, V. R.; Yang, B.; Rao, R. P.; Rasapalli, S.; Elfawal, M. A. Design, Synthesis, and Biological Evaluation of a Focused Pyrrolo- and Pyrido-Quinazolinone Natural Products-Templated Library for Anti-Fungal and Anthelmintic Activities. *Bioorg. Med. Chem.* **2026**, *134*, 118517. https://doi.org/10.1016/j.bmc.2025.118517

11a.2.24



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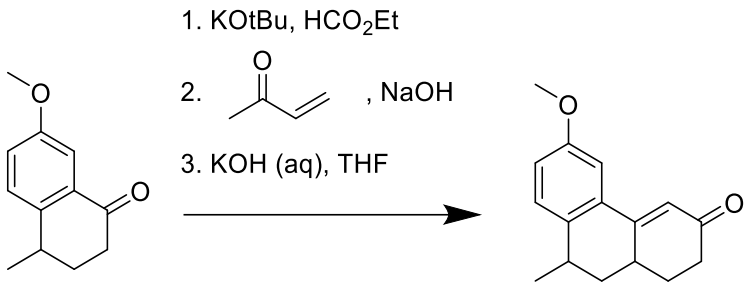
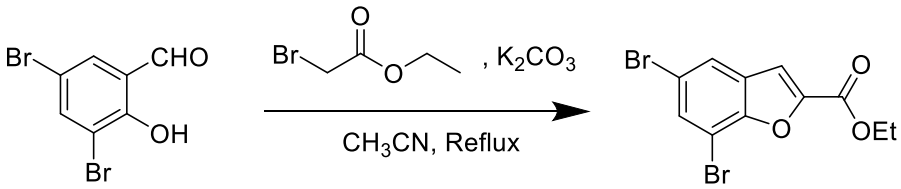


Roosen, P. C.; Karns, A. S.; Ellis, B. D.; Vanderwal, C. D. Evolution of a Short and Stereocontrolled Synthesis of (+)-7,20-Diisocyanoadociane. *J. Org. Chem.* **2022**, *87* (2), 1398–1420. https://doi.org/10.1021/acs.joc.1c02700

11a.2.26



Sulakhe, S. M.; Khanzode, A. K.; Jamale, S. E.; Singh, M. B.; Singh, P.; Kumari, J.; Sriram, D.; Vedpathak, S. G.; Haval, K. P. New Benzofuran-Triazole-Tetrazole Conjugates: Synthesis, Antitubercular Evaluation, Molecular Docking, DFT, and MD Simulation. *J. Mol. Struct*. **2027**, *1379*, 147348. https://doi.org/10.1016/j.molstruc.2026.147348

Section 11b: Alpha-Carbon Chemistry 2

Required foundation for this section:

Robinson annulation

Conjugated systems: 1,4-addition to conjugated dienes

Michael addition

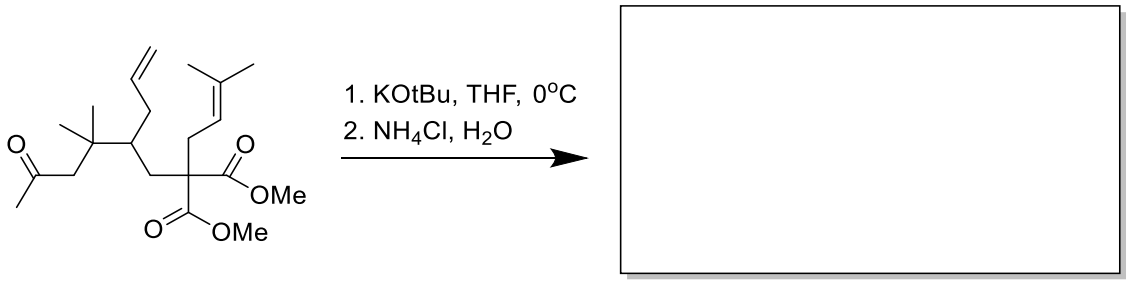
Gilman reagents

Stork enamine reaction

Section 11b – Box-Type Questions

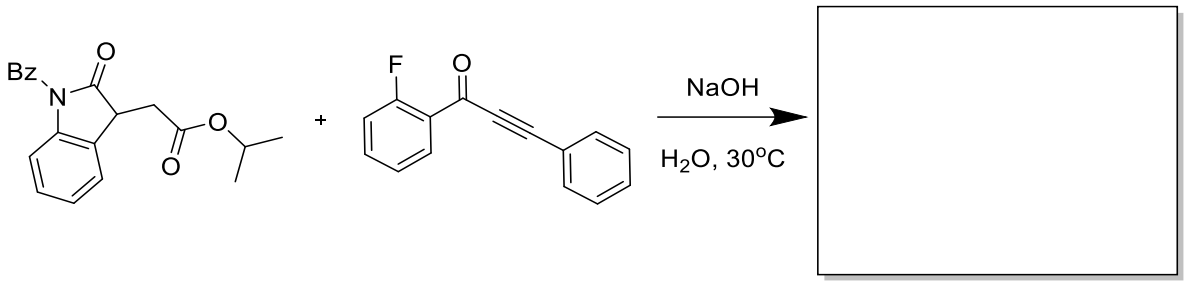
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

11b.1.1



Wan, Y.; Wu, H.; Xia, L.; Liu, S.; Ren, Y.; Xu, H.; Zheng, C. Sequential Dieckmann Cyclization Enables the Total Synthesis of 7- *Epi* -Clusianone and 18-Hydroxy-7- *Epi* -Clusianone. *Org. Biomol. Chem.* **2024**, *22* (3), 529–537. https://doi.org/10.1039/D3OB01840G

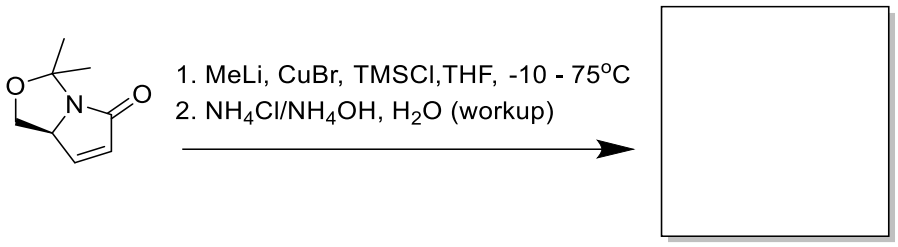
11b.1.2



Hint: A five-membered ring is formed.

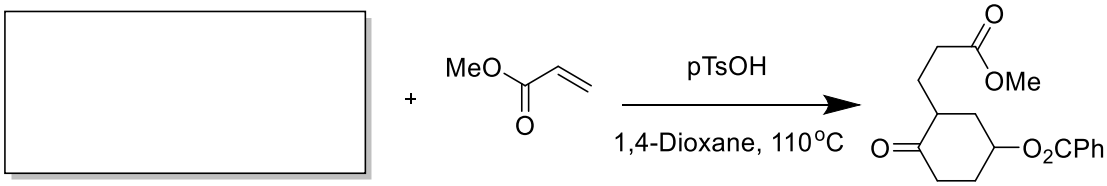
Lang, J.; Li, Y.; Kang, T.; Feng, X.; Liu, X. Organocatalytic Asymmetric Michael/Dieckmann Cyclization Reaction of Alkynones To Construct Spirocyclopentene Oxindoles. *Org. Lett.* **2019**, *21* (17), 6897–6902. https://doi.org/10.1021/acs.orglett.9b02519

11b.1.3



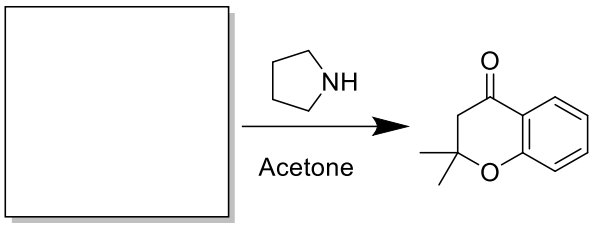
Wright, S. W.; Choi, C.; Chung, S.; Boscoe, B. P.; Drozda, S. E.; Mousseau, J. J.; Trzupek, J. D. Reversal of Diastereoselection in the Conjugate Addition of Cuprates to Unsaturated Lactams. *Org. Lett.* **2015***, 17* (21), 5204–5207. https://doi.org/10.1021/acs.orglett.5b02533

11b.1.4



Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in *sp*^{3}-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

11b.1.5



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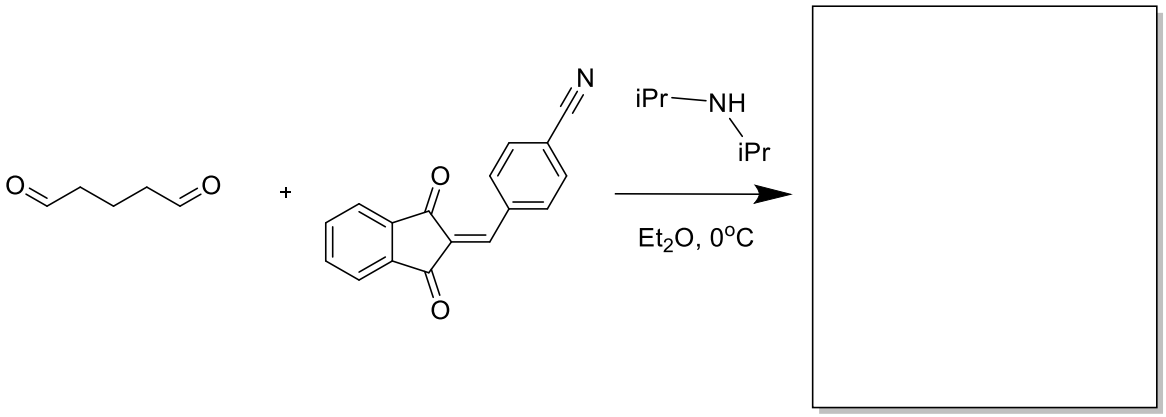
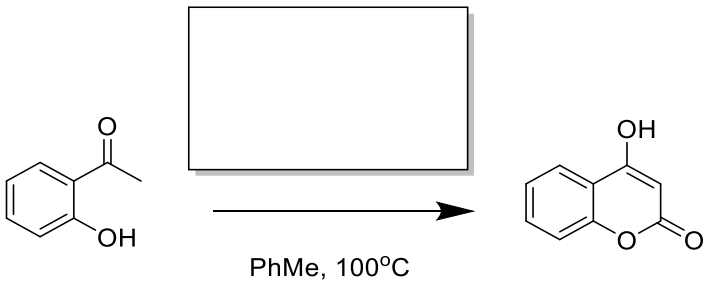
11b.1.6



Note: The authors used a chiral amine catalyst (absent from the reaction above to simplify the reaction) to achieve the desired stereochemistry of the product.

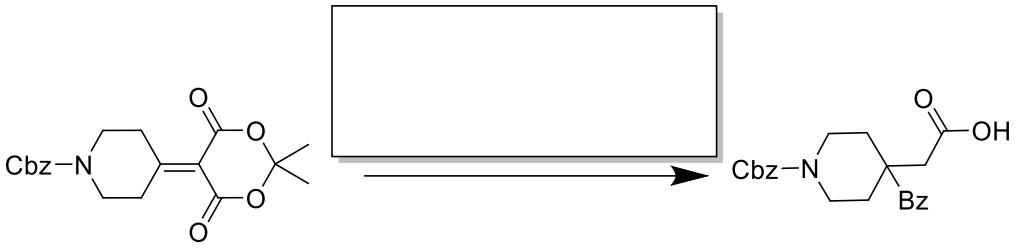
Anwar, S.; Li, S. M.; Chen, K. Organocatalytic Synthesis of Substituted Spirocyclohexane Carbaldehydes via [4 + 2] Annulation Strategy between 2-Arylideneindane-1,3-Diones and Glutaraldehyde. *Org. Lett.* **2014**, *16* (11), 2993–2995. https://doi.org/10.1021/ol501160k

11b.1.7



Aarjane, M.; Slassi, S.; Ait Mouha, M.; El-Ghayoury, A.; Yamni, K.; Amine, A. A New Coumarin Derivative: Synthesis, Crystal Structure, Computational Studies, and Dual Antioxidant–Antibacterial Activity. *J. Mol. Struct.* **2026**, *1349*, 143839. https://doi.org/10.1016/j.molstruc.2025.143839

11b.1.8



Chu, G.-H.; Le Bourdonnec, B.; Gu, M.; Saeui, C. T.; Dolle, R. E. General and Efficient Synthetic Approach to Novel Tricyclic Spiroketones. *Tetrahedron* **2009**, *65* (27), 5161-5167. https://doi.org/10.1016/j.tet.2009.04.094

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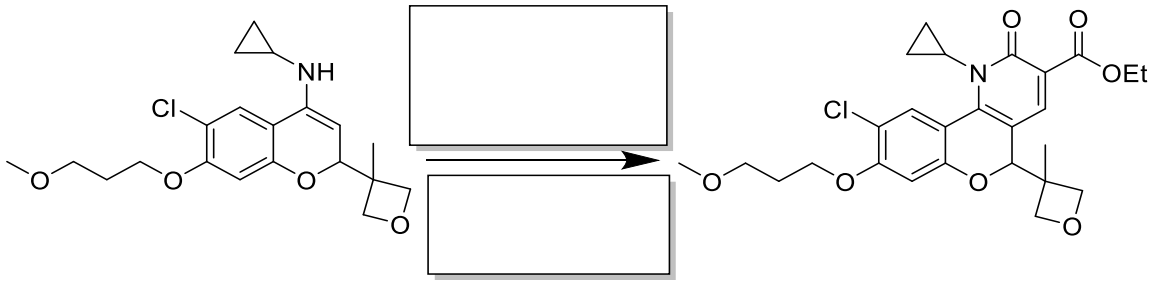

Mammoliti, O.; Palisse, A.; De Blieck, A.; Joannesse, C.; Allart, B.; Laruelle, C.; Jaunet, A.; De Munck, T.; Van der Plas, S.; Duthion, B.; Catana, C.; Christophe, T.; Houvenaghel, N.; Porte, V.; Jimenez, J.-M.; Beirinckx, F.; Iwens, A.; Chypre, M.; De Rijck, K.; Vandervoort, N.; Nelles, L.; Clément-Lacroix, P.; Delachaume, C.; Belleville, C.; Oste, L.; Borgonovi, M.; Wakselman, E.; Jans, M.; Hue-Perron, J.; Saniere, L.; Brys, R.; Andrews, M. Discovery and Characterization of GLPG3808, a PAPD5/7 Inhibitor for Suppression of Hepatitis B Viral Infections. *J. Med. Chem.* **2026**, *69* (3), 2006-2024. https://doi.org/10.1021/acs.jmedchem.5c01703

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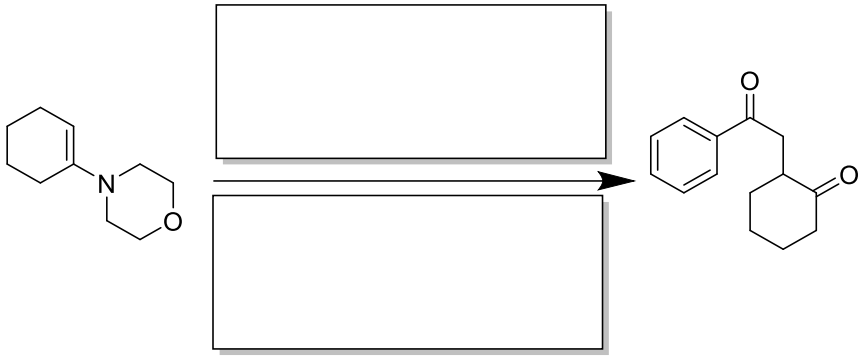
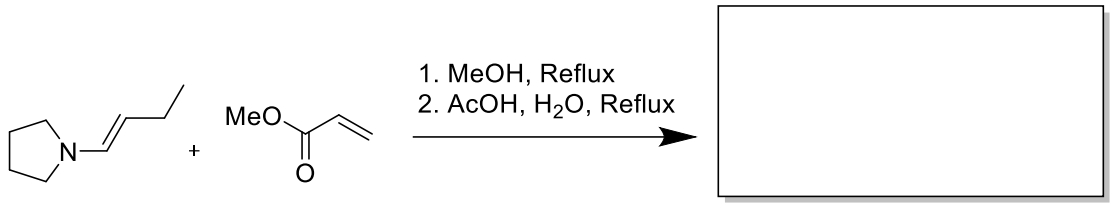


Pospelov, E. V.; Sukhorukov, A. Y. Accessing NH-Pyrrolidines from 1,4-Dicarbonyl Compounds via Catalytic Dioxime Cyclization. *J. Org. Chem.* **2026**, *91* (20), 7002-7012. https://doi.org/10.1021/acs.joc.6c00493

11b.1.11



Hint: The acid in step 2 is used to remove a functional group.

Zhang, L.; Lang, Y.; Luo, Z.; Han, X.; Zeng, H.; Li, C.-J. Precision Indole Skeletal Editing for Single-Carbon Replacement. *Science* **2026**, *392* (6797), 512-518. https://doi.org/10.1126/science.aec3587

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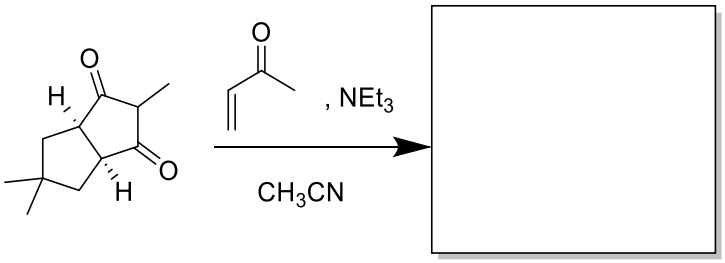
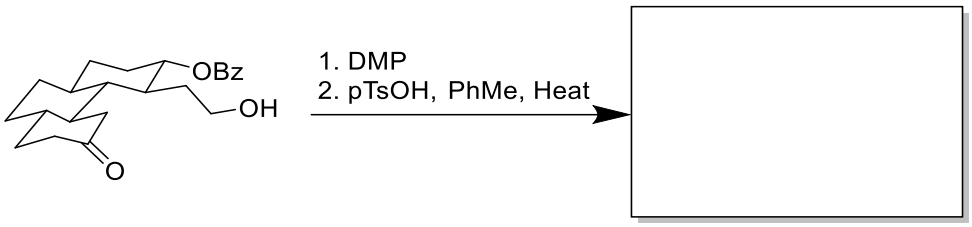


Siekmeyer, B.; Lübken, D.; Bajerke, K.; Bernhardt, B.; Schreiner, P. R.; Kalesse, M. Total Synthesis of (−)-Antroalbocin A Enabled by a Strain Release-Controlled Photochemical 1,3-Acyl Shift. *Org. Lett.* **2022**, *24* (31), 5812–5816. https://doi.org/10.1021/acs.orglett.2c02347

11b.1.13



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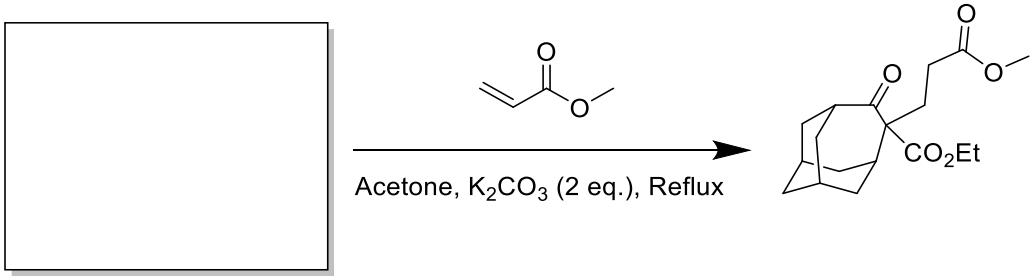
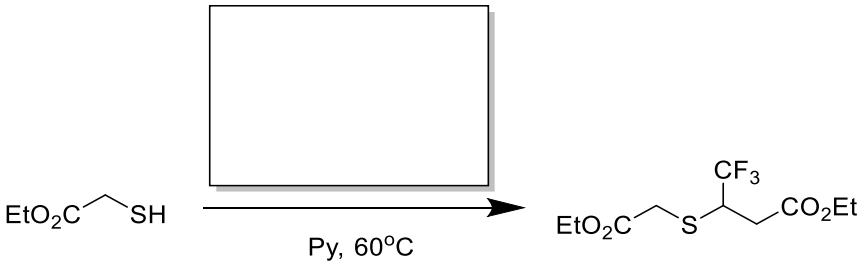
11b.1.14



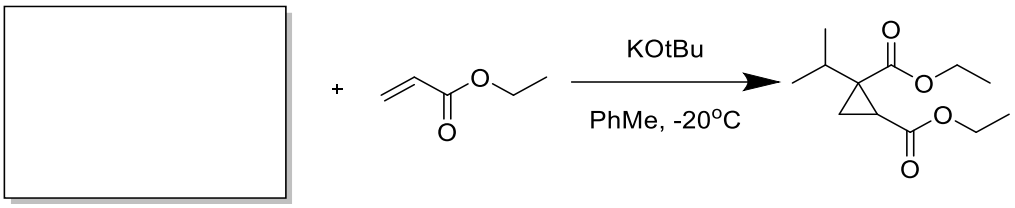
Tkachenko, I. M.; Mankova, P. A.; Rybakov, V. B.; Golovin, E. V.; Klimochkin, Y. N. Wagner–Meerwein Type Rearrangement in 5-Oxohomoadamantane Series. *Org. Biomol. Chem.* **2020**, *18* (3), 465–478. https://doi.org/10.1039/C9OB02060H

11b.1.15



Redka, M. O.; Dovhaniuk, N.; Blahun, O.; Liashuk, O. S.; Hurieva, A. M.; Lesyk, D.; Skrypnik, D.; Holota, Y.; Durylin, D.; Borysko, P.; Kondratov, I. S.; Grygorenko, O. O. Synthesis and Physicochemical Characterization of 5-Trifluoromethyl-Substituted Tetrahydrofurans and Tetrahydrothiophenes. *Eur. J. Org. Chem.* **2026**, *29* (3), e202501086. https://doi.org/10.1002/ejoc.202501086

11b.1.16



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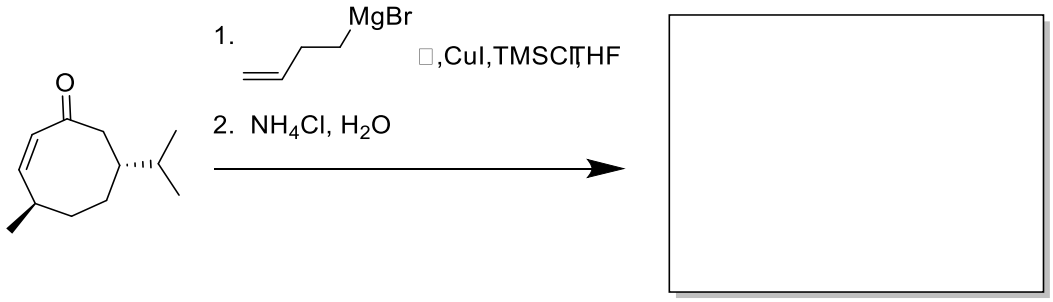
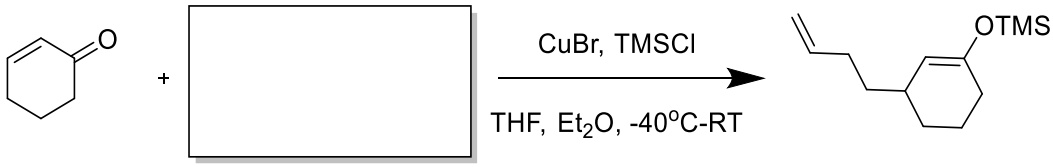


Note: Think carefully about the stereochemistry of the product.

Wang, X.-L.; Lu, Y.-Y.; Wang, J.; Wang, X.; Yao, H.-Q.; Lin, G.-Q.; Sun, B.-F. A Novel Synthetic Approach to the Bicyclo[5.3.1]undecan-11-one Framework of Vinigrol. *Org. Biomol. Chem.* **2014**, *12* (22), 3562-3566. https://doi.org/10.1039/C4OB00046C

11b.1.18



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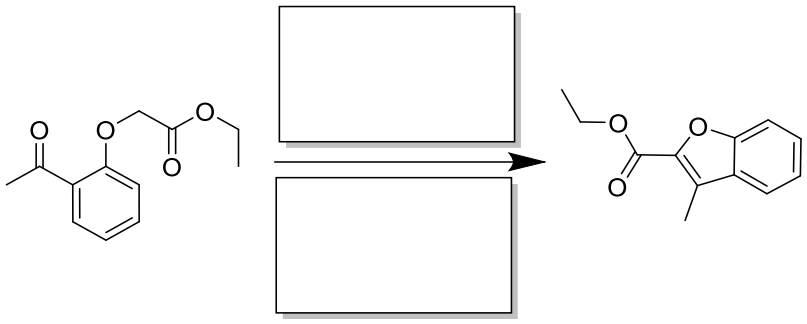
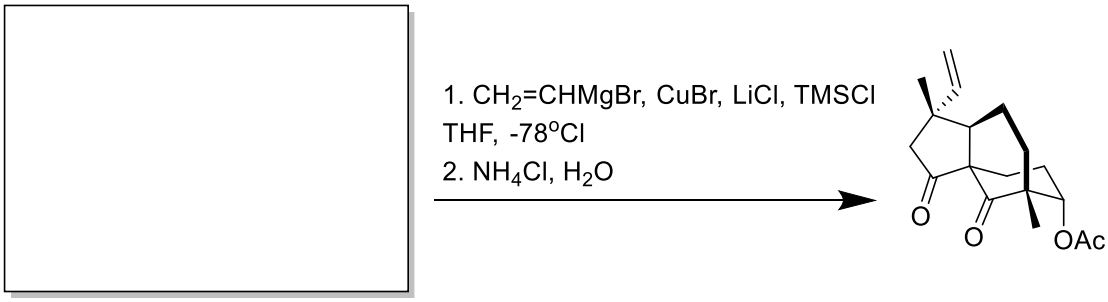
11b.1.19



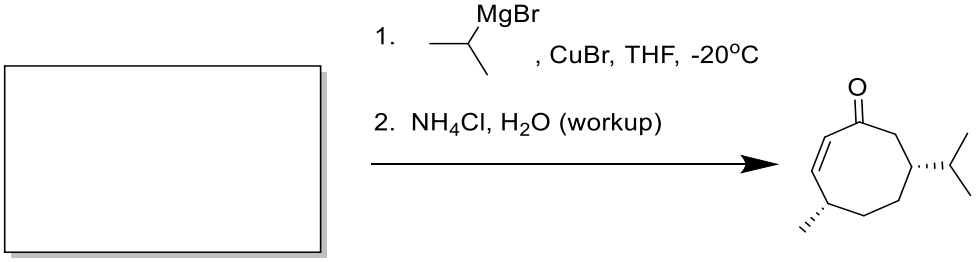
Eldehna, W. M.; Tawfik, H. O.; Nafie, M. S.; Al Kamaly, O.; El-Hamaky, A. A.; El Hassab, M. A.; Elsayed, Z. M.; Elnaggar, Y. S. R.; Al-Karmalawy, A. A.; Di Giacomo, V.; Balaha, M. Novel Benzofuran-Conjugated Indolin-2-Ones as Anticancer Agents: Design, Synthesis, Biological Assessments, and Molecular Modeling Insights. *Bioorg. Chem.* **2025**, *160*, 108494. https://doi.org/10.1016/j.bioorg.2025.108494

11b.1.20



Ninomiya, D.; Nagasawa, S.; Iwabuchi, Y. A Unified Approach to Highly Functionalized Clovane-Type Terpenoids: Enantiocontrolled Total Synthesis of Rumphellclovane E and Sarinfacetamides A and B. *Chem. Sci.* **2025**, *16* (34), 15707-15713. https://doi.org/10.1039/D5SC04197J

11b.1.21



Wang, X.-L.; Lu, Y.-Y.; Wang, J.; Wang, X.; Yao, H.-Q.; Lin, G.-Q.; Sun, B.-F. A Novel Synthetic Approach to the Bicyclo[5.3.1]undecan-11-one Framework of Vinigrol. *Org. Biomol. Chem.* **2014**, *12* (22), 3562-3566. https://doi.org/10.1039/C4OB00046C

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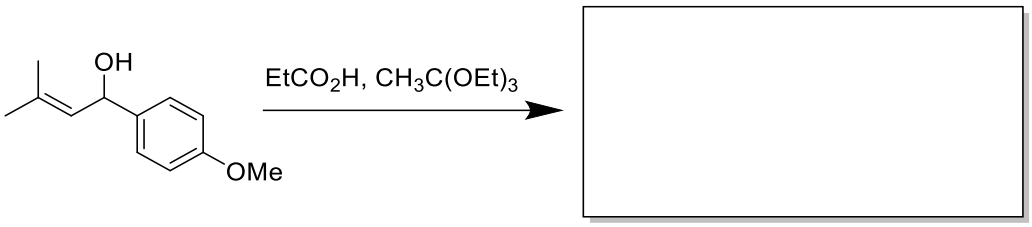

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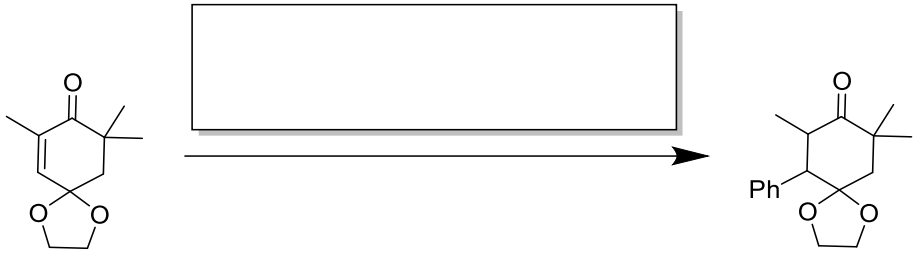
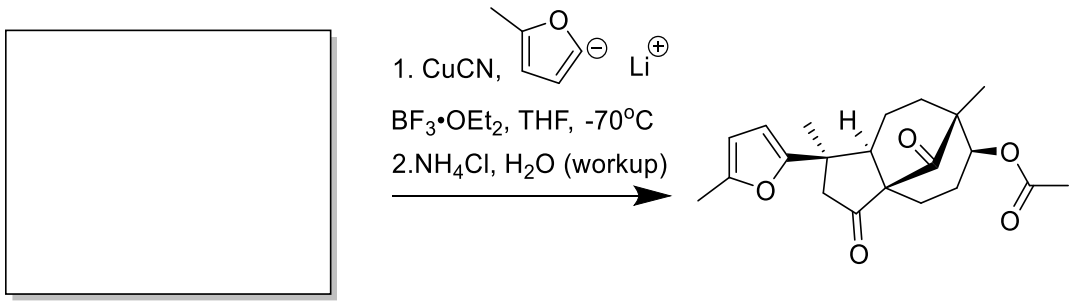
11b.1.23



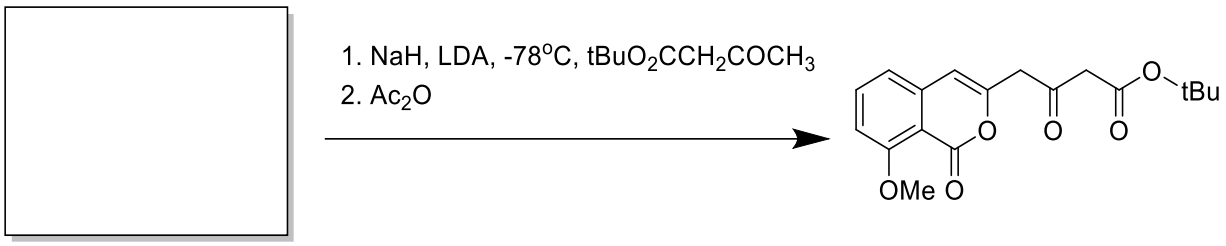
Xiong, J.; Wang, Y.; Tang, X. Binaphthalene-Modified C-Scorpionate Zinc Catalysts for Ring-Opening Polymerization of Bio-Based γ-Ketolactones to High-Molar-Mass Degradable Polyesters. *Angew. Chem. Int. Ed.* **2026**, *65* (3), e17535. https://doi.org/10.1002/anie.202517535

11b.1.24



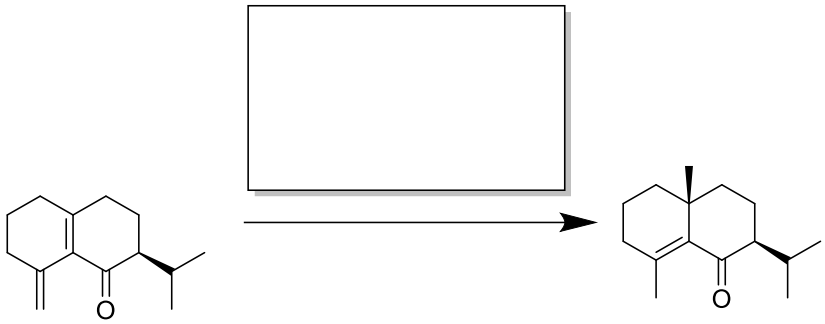
Ninomiya, D.; Nagasawa, S.; Iwabuchi, Y. A Unified Approach to Highly Functionalized Clovane-Type Terpenoids: Enantiocontrolled Total Synthesis of Rumphellclovane E and Sarinfacetamides A and B. *Chem. Sci.* **2025**, *16* (34), 15707-15713. https://doi.org/10.1039/D5SC04197J

11b.1.25



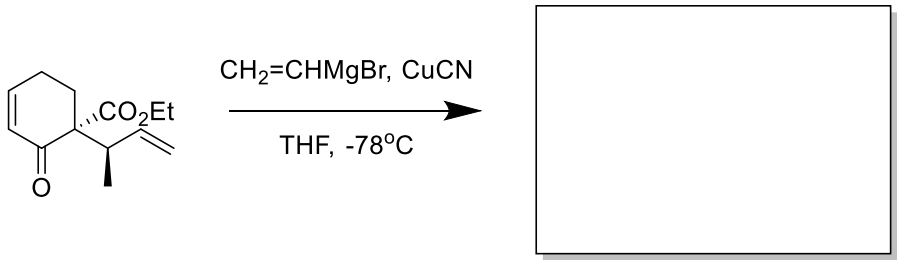
Zhou, J.-L.; Nie, Q.-Y.; Hou, X.-F.; Zheng, K.; Hong, R.; Tang, G.-L. Multienzyme Cascade Catalyzed Skeleton Rearrangement in a Caged Polyketide Biosynthesis. *Org. Lett.* **2025**, *27* (1), 376–380. https://doi.org/10.1021/acs.orglett.4c04412

11b.1.26



Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* **2009**, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

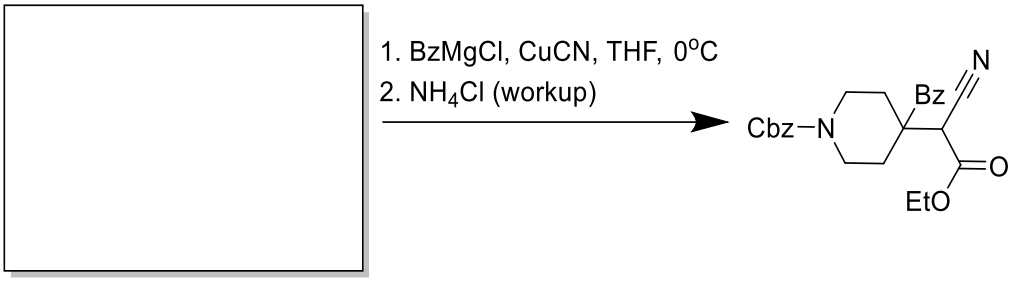
11b.1.27



Note: Assume the reaction is followed by an acidic workup.

Mao, H.-K.; Wang, Q.; Xu, J. Enantioselective Total Synthesis of Fortalpinoid Q via a TEMPO$^+$ BF_4^- - Mediated Dehydrative Nazarov Cyclization. *J. Am. Chem. Soc.* **2025**, *147* (11), 9079–9084. https://doi.org/10.1021/jacs.5c00319

11b.1.28



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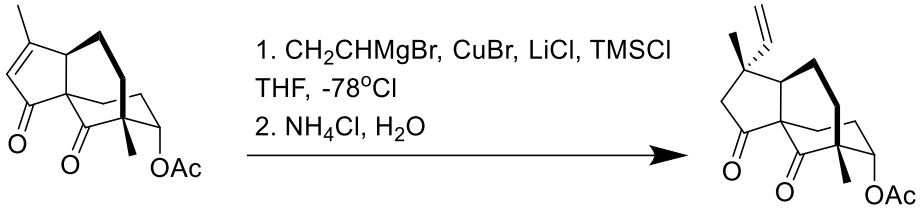
Section 11b – Mechanism Questions

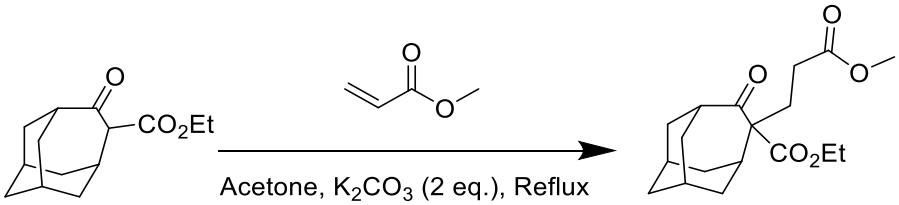
Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

11b.2.1



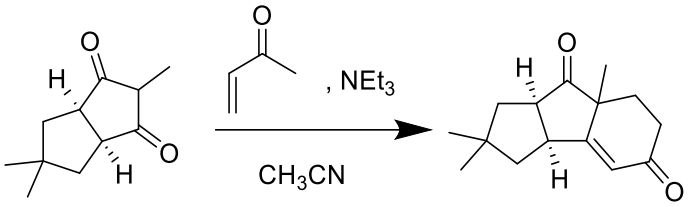
Ninomiya, D.; Nagasawa, S.; Iwabuchi, Y. A Unified Approach to Highly Functionalized Clovane-Type Terpenoids: Enantiocontrolled Total Synthesis of Rumphellclovane E and Sarinfacetamides A and B. *Chem. Sci.* **2025**, *16* (34), 15707-15713. https://doi.org/10.1039/D5SC04197J

11b.2.2



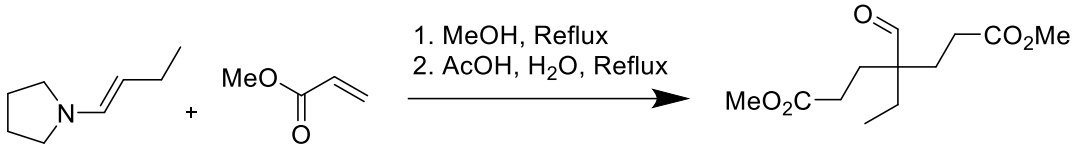
Tkachenko, I. M.; Mankova, P. A.; Rybakov, V. B.; Golovin, E. V.; Klimochkin, Y. N. Wagner–Meerwein Type Rearrangement in 5-Oxohomoadamantane Series. *Org. Biomol. Chem.* **2020**, *18* (3), 465–478. https://doi.org/10.1039/C9OB02060H

11b.2.3



Siekmeyer, B.; Lübken, D.; Bajerke, K.; Bernhardt, B.; Schreiner, P. R.; Kalesse, M. Total Synthesis of (−)-Antroalbocin A Enabled by a Strain Release-Controlled Photochemical 1,3-Acyl Shift. *Org. Lett.* **2022**, *24* (31), 5812–5816. https://doi.org/10.1021/acs.orglett.2c02347

11b.2.4



Zhang, L.; Lang, Y.; Luo, Z.; Han, X.; Zeng, H.; Li, C.-J. Precision Indole Skeletal Editing for Single-Carbon Replacement. *Science* **2026**, *392* (6797), 512-518. https://doi.org/10.1126/science.aec3587

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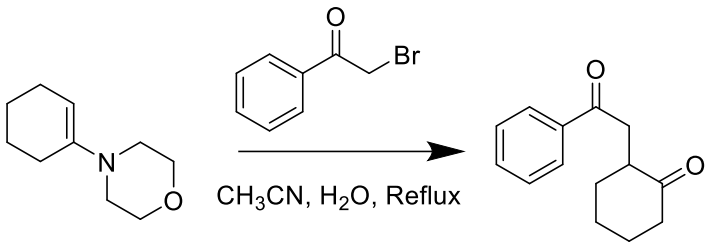
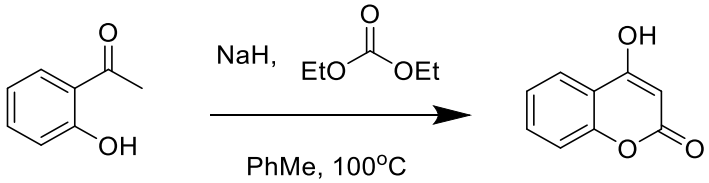


Pospelov, E. V.; Sukhorukov, A. Y. Accessing NH-Pyrrolidines from 1,4-Dicarbonyl Compounds via Catalytic Dioxime Cyclization. *J. Org. Chem.* **2026**, *91* (20), 7002-7012. https://doi.org/10.1021/acs.joc.6c00493

11b.2.6



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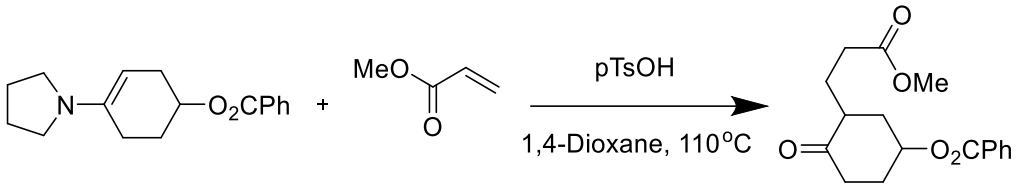
11b.2.7



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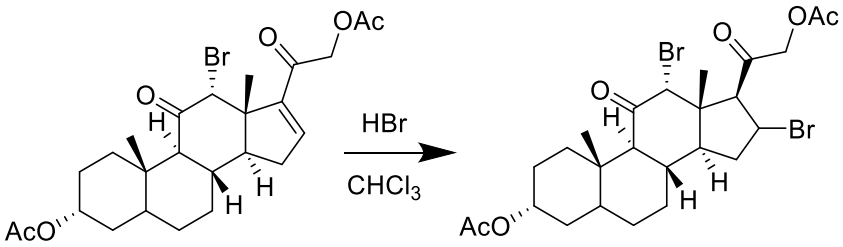
11b.2.8



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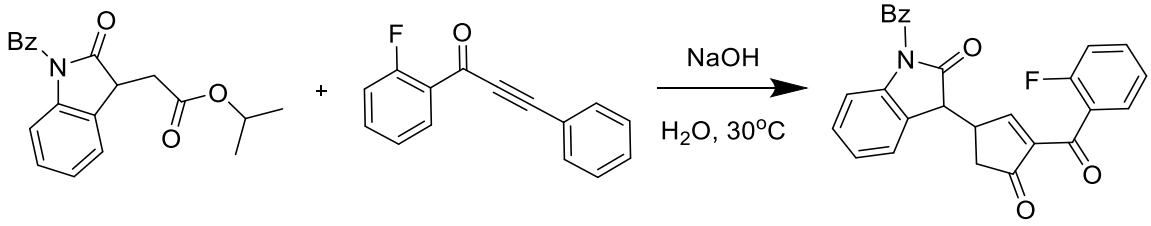
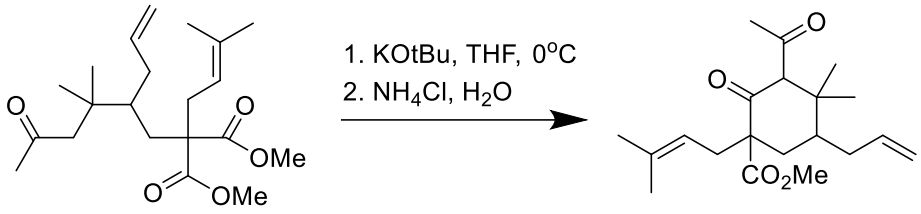
11b.2.9



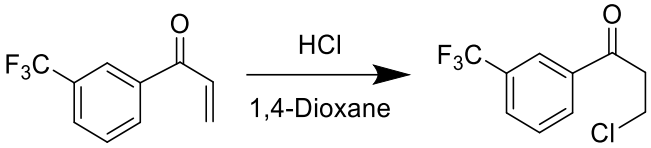
Lang, J.; Li, Y.; Kang, T.; Feng, X.; Liu, X. Organocatalytic Asymmetric Michael/Dieckmann Cyclization Reaction of Alkynones To Construct Spirocyclopentene Oxindoles. *Org. Lett.* **2019**, *21* (17), 6897–6902. https://doi.org/10.1021/acs.orglett.9b02519

11b.2.10



Wan, Y.; Wu, H.; Xia, L.; Liu, S.; Ren, Y.; Xu, H.; Zheng, C. Sequential Dieckmann Cyclization Enables the Total Synthesis of 7- *Epi* -Clusianone and 18-Hydroxy-7- *Epi* -Clusianone. *Org. Biomol. Chem.* **2024**, *22* (3), 529–537. https://doi.org/10.1039/D3OB01840G

11b.2.11



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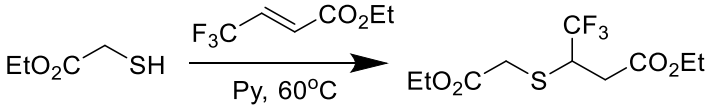

Redka, M. O.; Dovhaniuk, N.; Blahun, O.; Liashuk, O. S.; Hurieva, A. M.; Lesyk, D.; Skrypnik, D.; Holota, Y.; Durylin, D.; Borysko, P.; Kondratov, I. S.; Grygorenko, O. O. Synthesis and Physicochemical Characterization of 5-Trifluoromethyl-Substituted Tetrahydrofurans and Tetrahydrothiophenes. *Eur. J. Org. Chem.* **2026**, *29* (3), e202501086. https://doi.org/10.1002/ejoc.202501086

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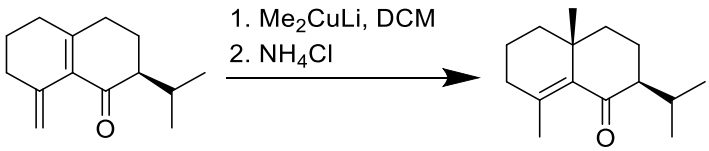

Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* **2009**, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

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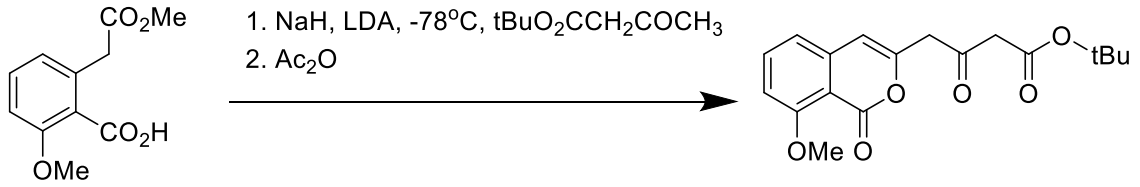

Zhou, J.-L.; Nie, Q.-Y.; Hou, X.-F.; Zheng, K.; Hong, R.; Tang, G.-L. Multienzyme Cascade Catalyzed Skeleton Rearrangement in a Caged Polyketide Biosynthesis. *Org. Lett.* **2025**, *27* (1), 376–380. https://doi.org/10.1021/acs.orglett.4c04412

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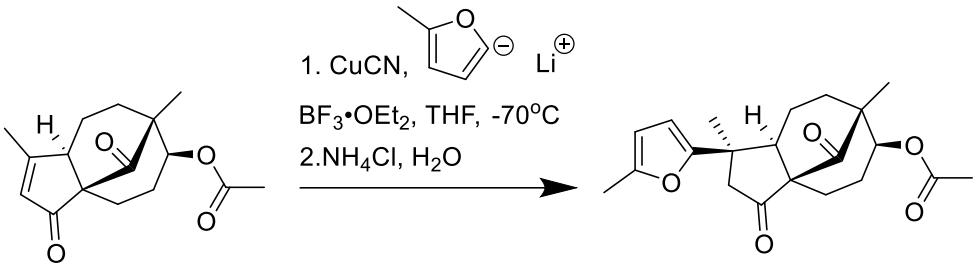

Ninomiya, D.; Nagasawa, S.; Iwabuchi, Y. A Unified Approach to Highly Functionalized Clovane-Type Terpenoids: Enantiocontrolled Total Synthesis of Rumphellclovane E and Sarinfacetamides A and B. *Chem. Sci.* **2025**, *16* (34), 15707-15713. https://doi.org/10.1039/D5SC04197J

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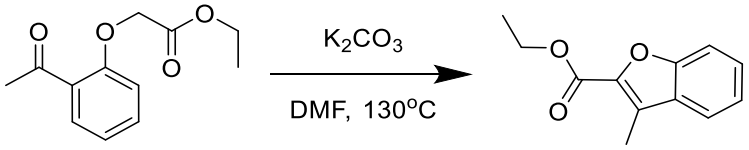

Eldehna, W. M.; Tawfik, H. O.; Nafie, M. S.; Al Kamaly, O.; El-Hamaky, A. A.; El Hassab, M. A.; Elsayed, Z. M.; Elnaggar, Y. S. R.; Al-Karmalawy, A. A.; Di Giacomo, V.; Balaha, M. Novel Benzofuran-Conjugated Indolin-2-Ones as Anticancer Agents: Design, Synthesis, Biological Assessments, and Molecular Modeling Insights. *Bioorg. Chem.* **2025**, *160*, 108494. https://doi.org/10.1016/j.bioorg.2025.108494

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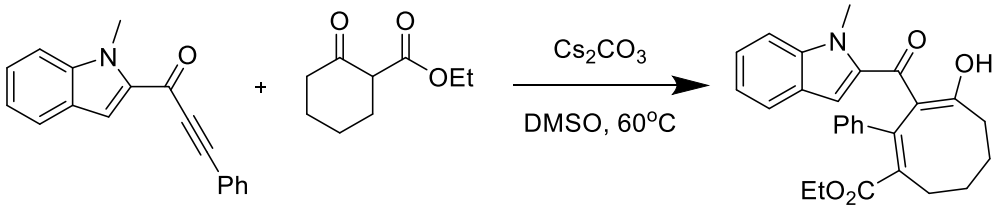

Matsui, J. K.; Molander, G. A. Organocatalyzed, Photoredox Heteroarylation of 2-Trifluoroboratochromanones via C–H Functionalization. *Org. Lett.* **2017**, *19* (4), 838–841. https://doi.org/10.1021/acs.orglett.7b00196

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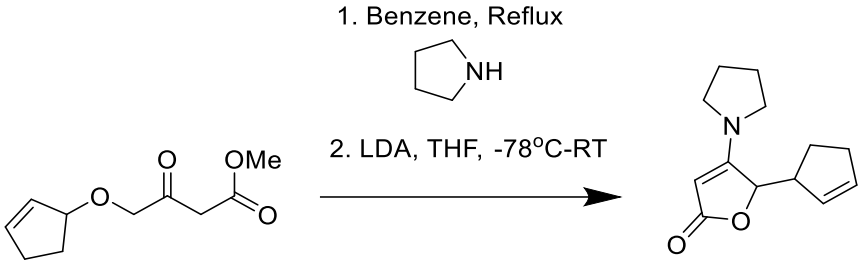

Ho, G.-M.; Tseng, C.-W.; Liu, Y.-H.; Li, Y.-J. Direct Synthesis of 5-Cycloalkene-Substituted γ-Butenolides via [2,3]-Wittig Rearrangement of Vinylogous Urethanes. *Synth. Commun.* **2026**, *56* (4), 318-327. https://doi.org/10.1080/00397911.2026.2621827

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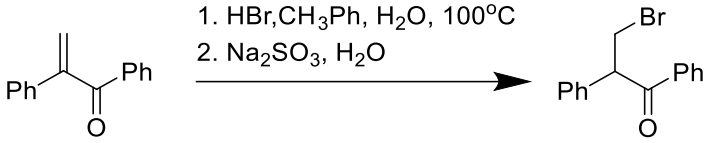

Cruz, C.; Galicia, J.; Bowers, S.; Hua, J.; Romero, E. A. Visible Light-Driven Contra-Thermodynamic Functional Group Transposition of Chalcones. *J. Am. Chem. Soc.* **2026**, *148* (1), 801-808. https://doi.org/10.1021/jacs.5c16361

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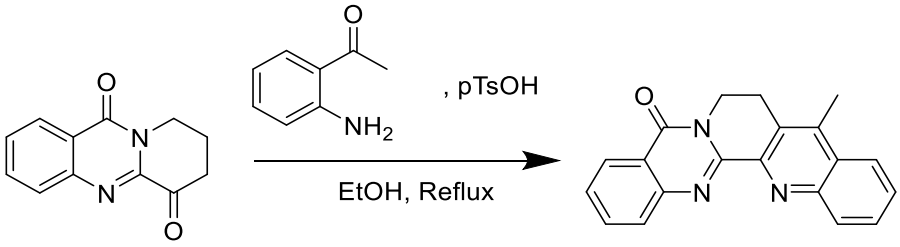

D'Almeida, R. E.; Chen, P.; Huang, Y.; Goetz, E.; Sammeta, V. R.; Yang, B.; Rao, R. P.; Rasapalli, S.; Elfawal, M. A. Design, Synthesis, and Biological Evaluation of a Focused Pyrrolo- and Pyrido-Quinazolinone Natural Products-Templated Library for Anti-Fungal and Anthelmintic Activities. *Bioorg. Med. Chem.* **2026**, *134*, 118517. https://doi.org/10.1016/j.bmc.2025.118517

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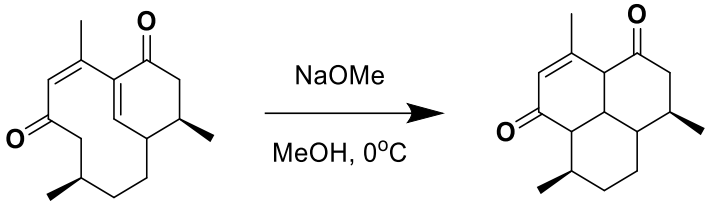

Ramella, V.; Roosen, P. C.; Vanderwal, C. D. Concise Formal Synthesis of the Pseudopterosins via Anionic Oxy-Cope/Transannular Michael Addition Cascade. *Org. Lett*. **2020**, *22* (8), 2883–2886. https://doi.org/10.1021/acs.orglett.0c00486

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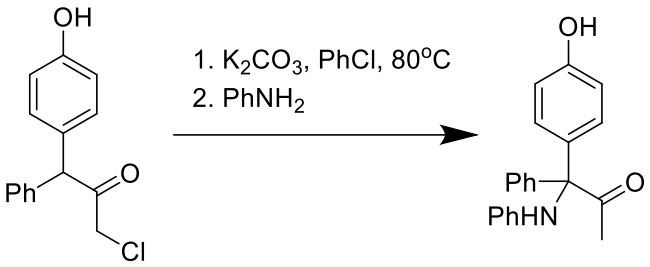
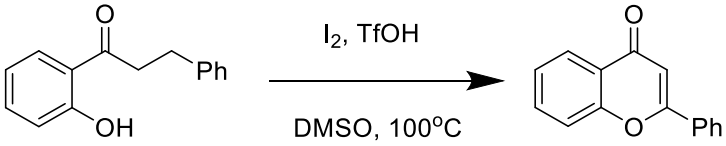


Hint: There is an intramolecular S_N2 in the reaction mechanism.

Su, Z.-Y.; Zhang, Y.-R.; Luo, J.-H.; Huang, X.; Li, B.-Q.; Ma, A.-J.; Zhang, X.-Z. Oxidant-Free α-Amination of Ketones with Nitrogen Nucleophiles. *J. Org. Chem*. **2026**, *91* (26), 9070–9079. https://doi.org/10.1021/acs.joc.6c00783

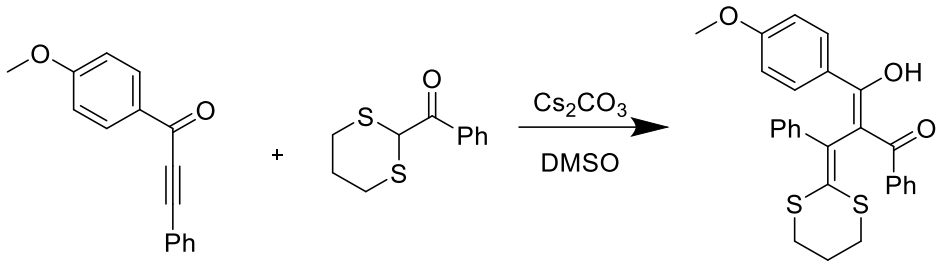
11b.2.23



Hint: The first three steps are likely: alpha halogenation, elimination, Michael addition.

Mao, H.-X.; Zhao, B.-Y.; Kou, L.-G.; Zou, B.-X.; Wang, Y.-Q. Iodine-Catalyzed Carbonyl Desaturation: A One-Pot Synthesis of Flavones. *J. Org. Chem*. **2026**, *91* (31), 10702–10708. https://doi.org/10.1021/acs.joc.6c01237

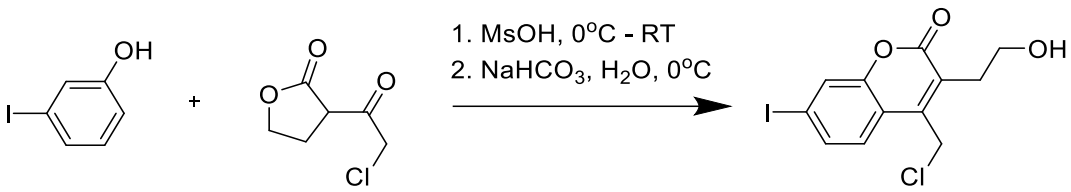
11b.2.24



Hint: At some point in the mechanism, a four membered ring is formed.

Yang, Y.; Cheng, L.; Wang, M.; Yin, L.; Feng, Y.; Wang, C.; Li, Y. Difunctionalization of Alkynones by Base-Mediated Reaction with α,α-Dithioketones. *Org. Lett*. **2021**, *23* (14), 5339–5343. https://doi.org/10.1021/acs.orglett.1c01640

11b.2.25



Masai, H.; Niikura, N.; Russell, G. M.; Kawano, Y.; Tsuda, S.; Iwai, T.; Terao, J. Supramolecular Conformational Control of Photolability in Polymer Networks Crosslinked with a Kinetically Stable Pseudo[1]rotaxane Based on a Coumarinylmethyl Ester. *Chem. Sci.* **2025**, *16* (36), 16737–16743. https://doi.org/10.1039/D5SC01641J

Section 12: Amines

Required foundation for this section:

Synthesis of amines

Primary amine synthesis

Reductive amination

Reactions of amine group

Diazotization of primary aryl amines

Mannich reaction

Sandmeyer reactions

Azo coupling

Hofmann elimination

Amine oxidation and then elimination (Cope elimination)

Reduction of amides (covered in Section 10b)

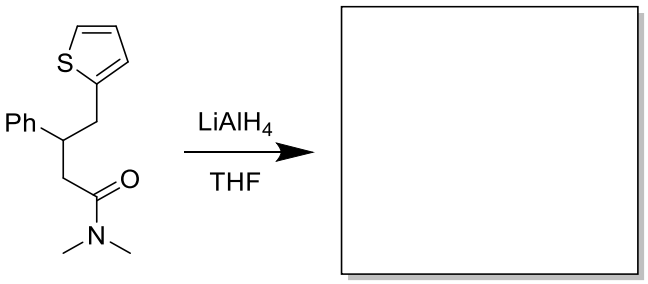
Reduction of nitriles (covered in Section 10b)

Hydrolysis of nitriles (covered in Section 10b)

Section 12 – Box-Type Questions

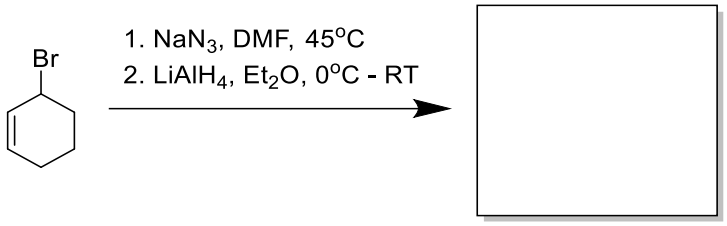
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

12.1.1



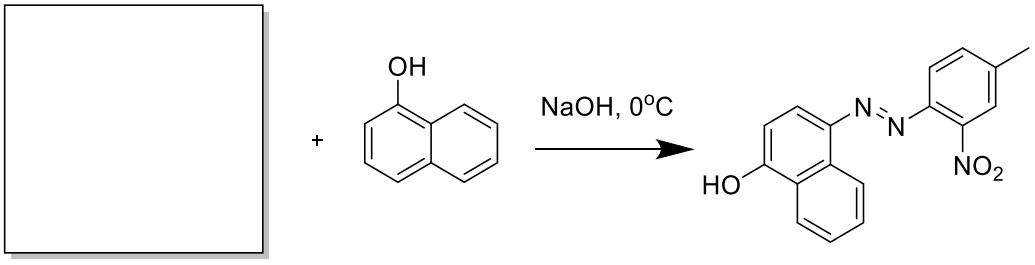
Gu, Y.; Ma, R.; Zuo, S.; Liu, G.; Li, G.; Yu, R.; Xiong, D.; Xu, X.; Walsh, P. J.; Mao, J. Raising the *p*K_a_ Limit of Pronucleophiles in 1,4-Additions via Heterobimetallic Alkali-Metal Catalysis. *ACS Catal.* **2026**, *16* (9), 8619-8632. https://doi.org/10.1021/acscatal.6c01195

12.1.2



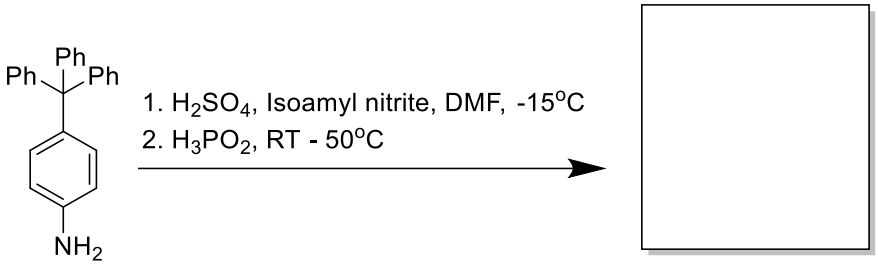
Nguyen, S. T.; Zhu, Q.; Knowles, R. R. PCET-Enabled Olefin Hydroamidation Reactions with *N*-Alkyl Amides. *ACS Catal.* **2019**, *9* (5), 4502-4507. https://doi.org/10.1021/acscatal.9b00966

12.1.3



Razeghi, R.; Kazemi, F.; Kaboudin, B.; Olyaei, A.; Yokomatsu, T. Synthesis and Characterization of Novel Photochromic and pH-Sensitive Colorimetric Hydrogel Based on Azobenzene. *Can. J. Chem.* **2021**, *99* (4), 368-381. https://doi.org/10.1139/cjc-2020-0369

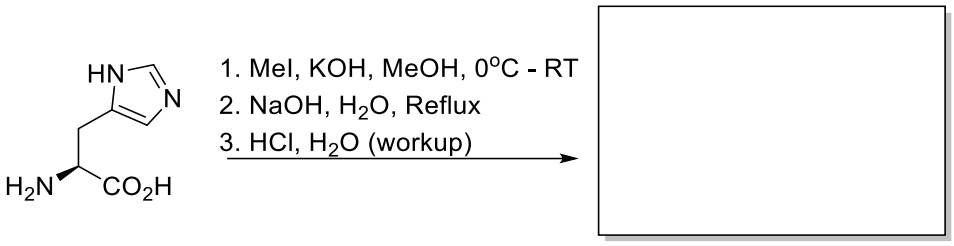
12.1.4



Note: Isoamyl nitrite is analogous to sodium nitrite.

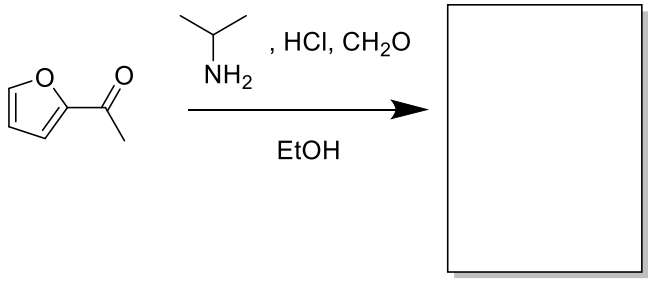
Bulut, A.; Doğan, N.; Kirpi, E.; Zorlu, Y.; Yücesan, G. A Systematic Look at Structural Diversity of Metal Phosphonates. *Eur. J. Inorg. Chem.* **2024**, *27* (13), e202300699. https://doi.org/10.1002/ejic.202300699

12.1.5



Valeev, F. A.; Salikhov, Sh. M.; Krasnoslobodtseva, O. Y.; Sharipov, B. T.; Spirikhin, L. V.; Tolstikov, G. A. Synthesis of *N*-Methyl Urocanates of Hydroxyderivatives of Isocembrol. *Chem. Nat. Compd.* **2007**, *43* (2), 143-148. https://doi.org/10.1007/s10600-007-0065-6

12.1.6

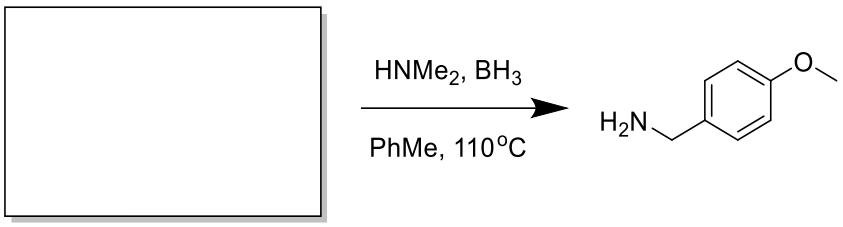


Note: Assume there was a basic workup following the reaction.

Lewis, D.; Zhang, Y.; Prisinzano, T.; Dersch, C. M.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. Further Exploration of 1-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}piperazine (GBR 12909): Role of N-Aromatic, N-Heteroaromatic, and 3-Oxygenated N-phenylpropyl Substituents on Affinity for the Dopamine and

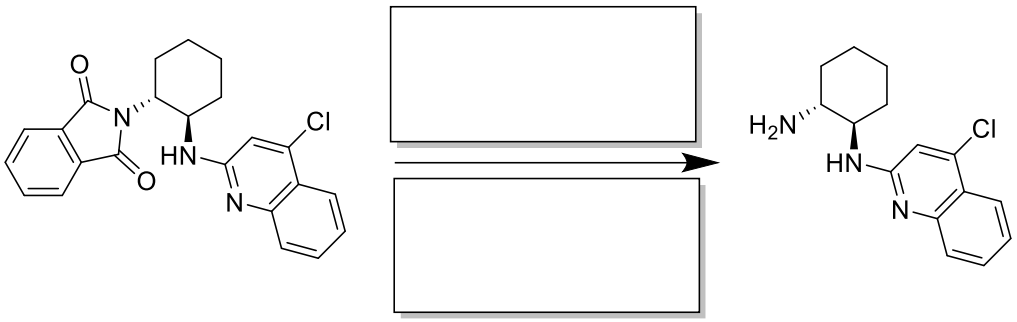
Serotonin Transporter. *Bioorg. Med. Chem. Lett.* **2003**, *13* (7), 1385–1389. https://doi.org/10.1016/S0960-894X(03)00108-2

12.1.7



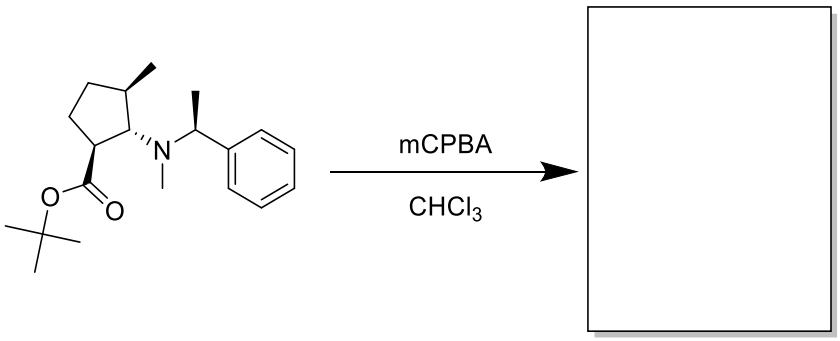
Chowdhury, D.; Mukherjee, A. Unlocking an Additive-Free and Catalyst-Free Dual Approach for Reduction of Amides to Amines. *Chem. Commun.* **2025**, *61* (8), 1605-1608. https://doi.org/10.1039/D4CC04606D

12.1.8



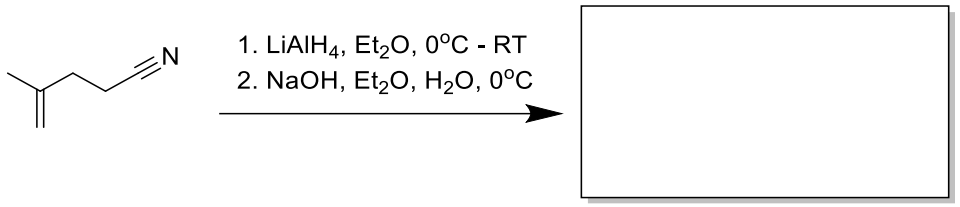
Toldo, S.; Poletti, L.; Di Carmine, G.; Bortolini, O.; De Risi, C.; Felletti, S.; Compagnin, G.; Massi, A.; Ragno, D. Effective and Practical Stereoselective Synthesis of Nutlins Precursors by Immobilization of Privileged Chiral Mono-Amidine Catalyst. *Adv. Synth. Catal.* **2025**, *367* (9), e202500058. https://doi.org/10.1002/adsc.202500058

12.1.9



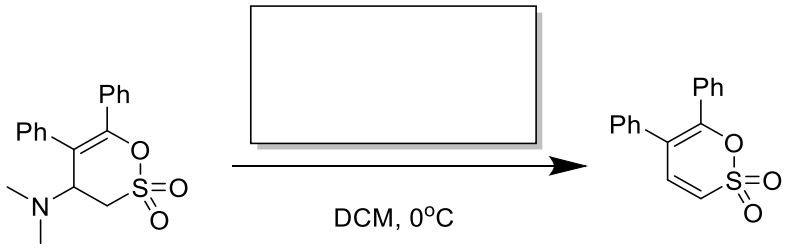
Bunnage, M. E.; Chippindale, A. M.; Davies, S. G.; Parkin, R. M.; Smith, A. D.; Withey, J. M. Asymmetric Synthesis of (1R,2S,3R)-3-Methylcispentacin and (1S,2S,3R)-3-Methyltranspentacin by Kinetic Resolution of *tert*-Butyl (±)-3-Methylcyclopentene-1-carboxylate. *Org. Biomol. Chem.* **2003**, *1* (21), 3698-3707. https://doi.org/10.1039/B306935B

12.1.10



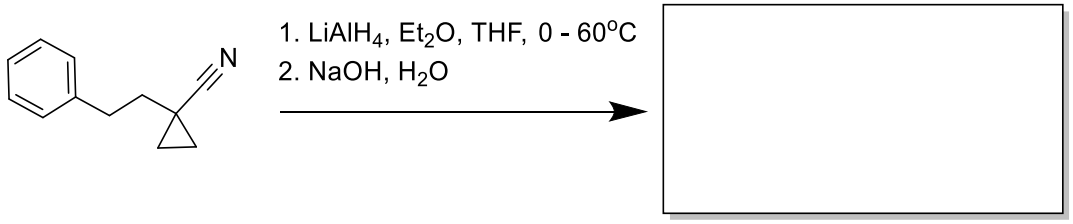
Nguyen, S. T.; Zhu, Q.; Knowles, R. R. PCET-Enabled Olefin Hydroamidation Reactions with *N*-Alkyl Amides. *ACS Catal.* **2019**, *9* (5), 4502-4507. https://doi.org/10.1021/acscatal.9b00966

12.1.11



Aiken, S.; Anozie, K.; de Azevedo, O. D. C. C.; Cowen, L.; Edgar, R. J. L.; Gabbutt, C. D.; Heron, B. M.; Lawrence, P. A.; Mills, A. J.; Rice, C. R.; Urquhart, M. W. J.; Zonidis, D. Expedient Synthesis of Highly Substituted 3,4-Dihydro-1,2-oxathiine 2,2-Dioxides and 1,2-Oxathiine 2,2-Dioxides: Revisiting Sulfene Additions to Enaminoketones. *Org. Biomol. Chem.* **2019**, *17* (44), 9585-9604. https://doi.org/10.1039/C9OB01657K

12.1.12



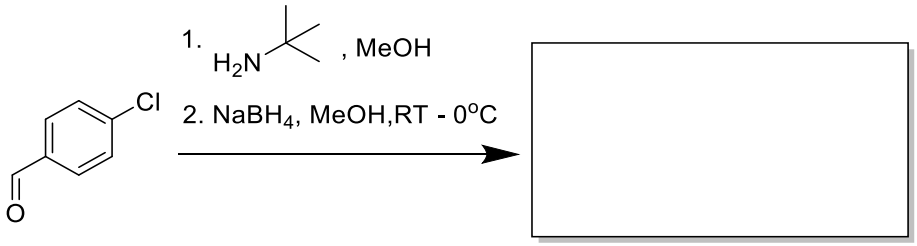
Zhu, S.; Zhu, P.; Chen, S.; Gao, M.; Jiang, L.; Liu, T.; Yu, H.; Han, Y.; Hou, H. Intramolecular Oxidative C(sp^3)-N Coupling toward Pyrrolidine and Piperidine with a Catalytic Amount of Iodoform. *Chem. Commun.* **2026**, *62* (48), 12148-12151. https://doi.org/10.1039/D6CC02334G

12.1.13



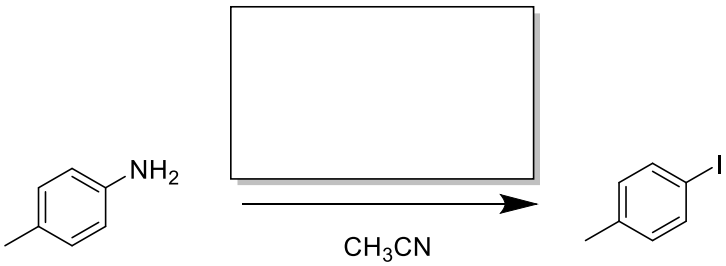
Qi, J.; Wang, C.; Wang, G.; O'Neill, P.; Reddy Dubbaka, S.; Ting Ang, H.; Chen, X.; Wu, J. Strain-Release-Driven Electrochemical Skeletal Rearrangement of Non-Biased Alkyl Cyclopropanes/Butanes. *Angew. Chem. Int. Ed.* **2025**, *64* (1), e202413723. https://doi.org/10.1002/anie.202413723

12.1.14



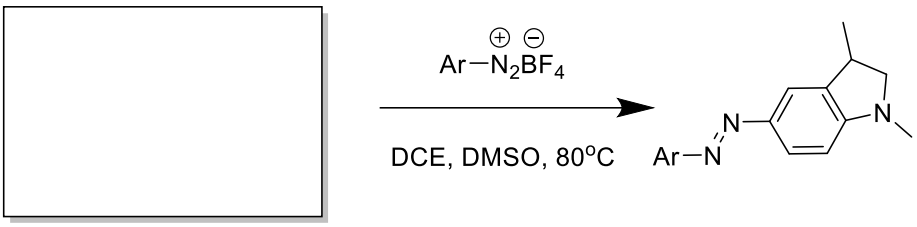
Mo, S.; Xu, J. Chemospecific Intramolecular Buchner Reaction Catalyzed by Copper(II) Acetylacetonate. *ChemCatChem* **2014**, *6* (6), 1679-1683. https://doi.org/10.1002/cctc.201400014

12.1.15



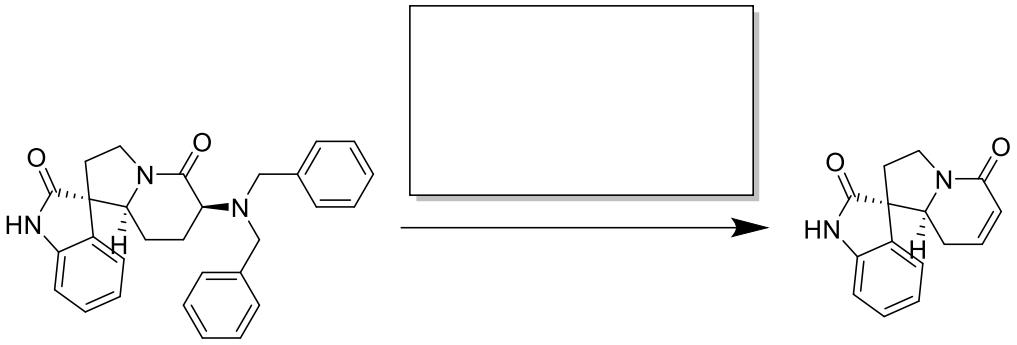
Zhao, Y.-L.; An, J.-X.; Yang, F.-F.; Guan, X.; Fu, X.-Z.; Li, Z.-Q.; Wang, D.-P.; Zhou, M.; Yang, Y.-Y.; He, B. One-Pot Asymmetric Oxidative Dearomatization of 2-Substituted Indoles by Merging Transition Metal Catalysis with Organocatalysis to Access C2-Tetrasubstituted Indolin-3-Ones. *Adv. Synth. Catal.* **2022**, *364* (7), 1277-1285. https://doi.org/10.1002/adsc.202101498

12.1.16



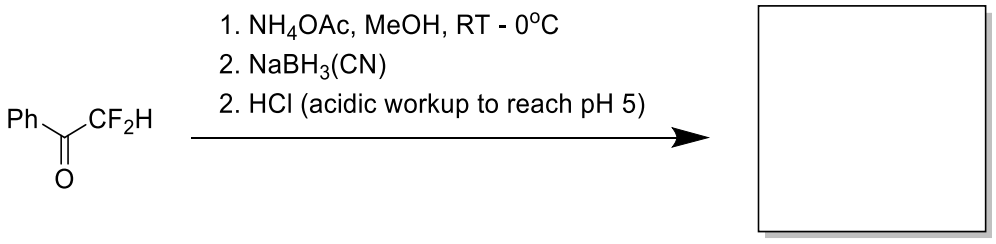
Liu, Y.; Zhang, P.; Feng, L.; Zhang, Z.; Liang, T. Transition-Metal-Free Synthesis of C3,5-Difunctionalized Oxindole Derivatives. *Org. Chem. Front.* **2025**, *12* (8), 2704-2708. https://doi.org/10.1039/D4QO02428A

12.1.17



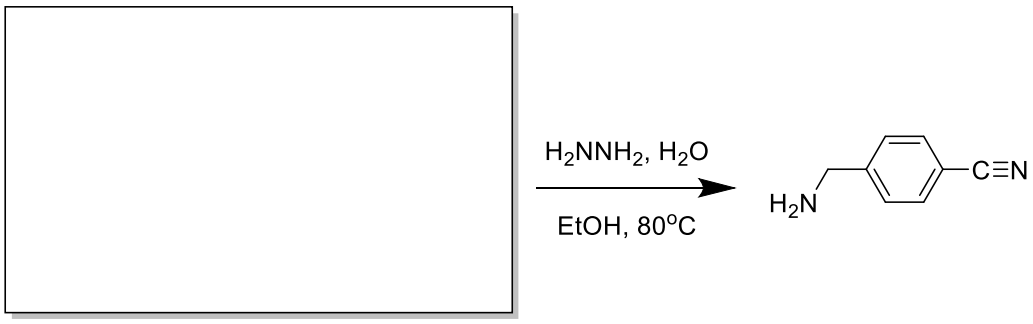
Kuntiyong, P.; Inprung, N.; Phakdeeyothin, K.; Buaphan, A.; Thammapichai, K. Synthesis of Spiro[indolizidine-1,3′-oxindole] from *L*-Glutamic Acid. *Tetrahedron* **2020**, *76* (24), 131261. https://doi.org/10.1016/j.tet.2020.131261

12.1.18



Das, S.; Maity, D.; Paul, B.; Patel, S.; Chatterjee, I. Access to Alkylative/Hydrodefluorination of Trifluoromethyl Ketones Using Photoexcited Dihydropyridines. *Org. Lett.* **2026**, *28* (2), 813-818. https://doi.org/10.1021/acs.orglett.5c04969

12.1.19



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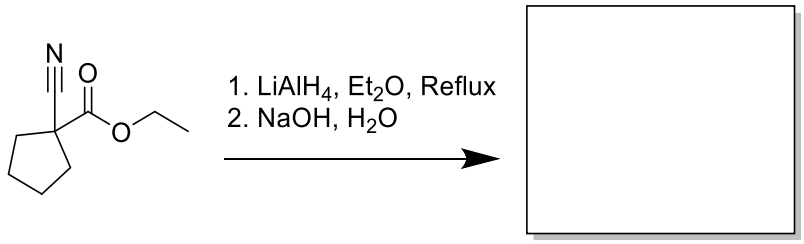

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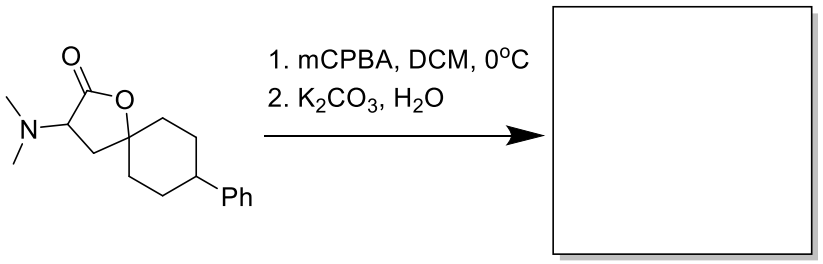

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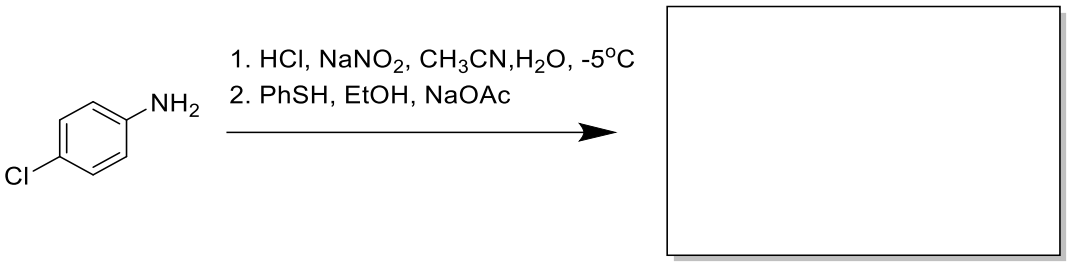

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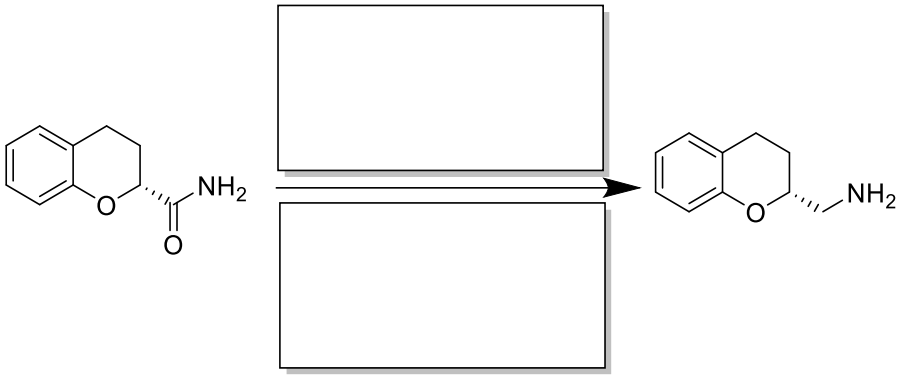

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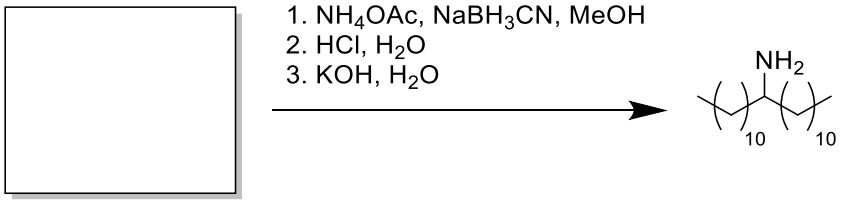

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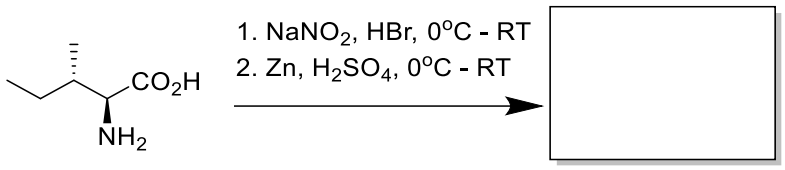

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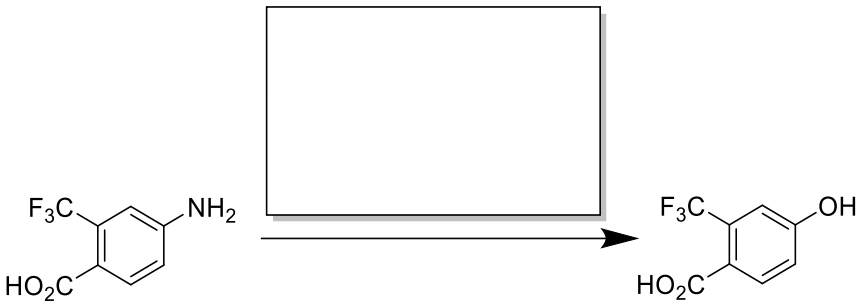

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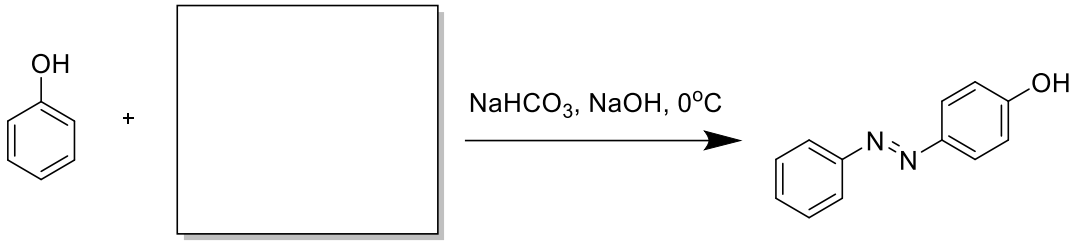

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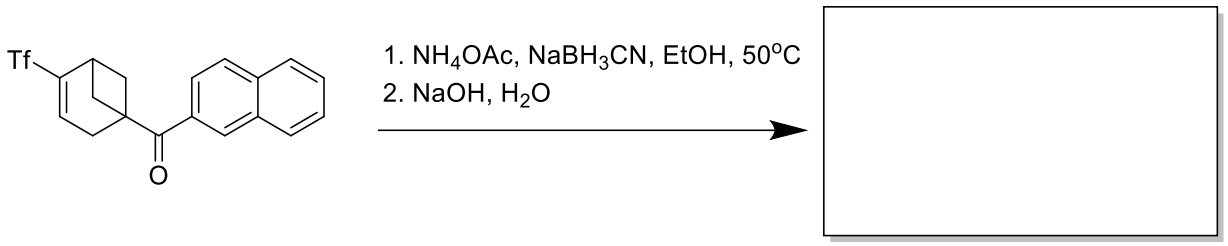

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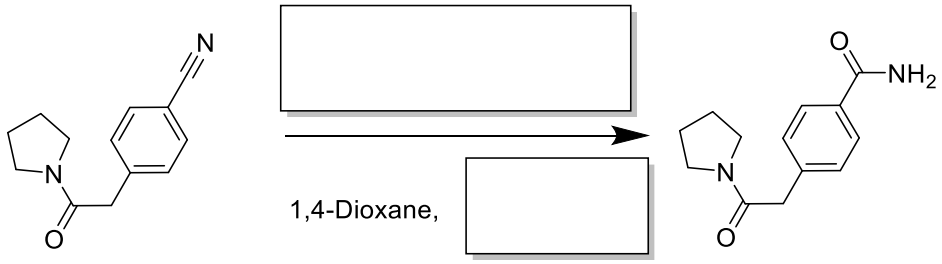

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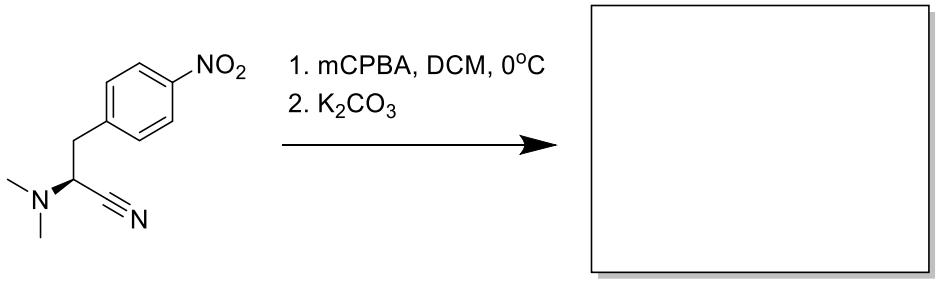

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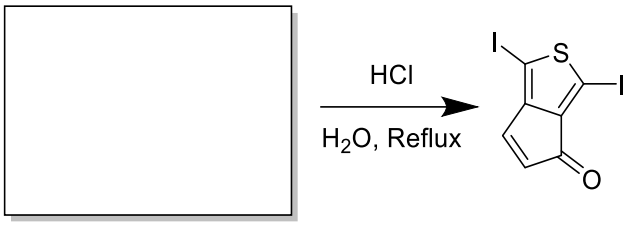

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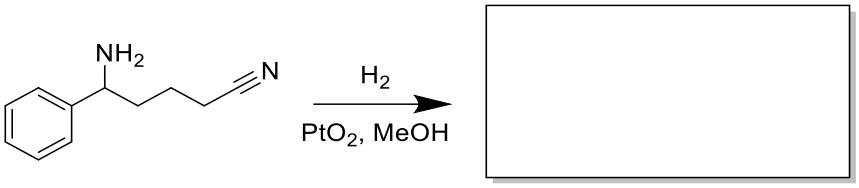

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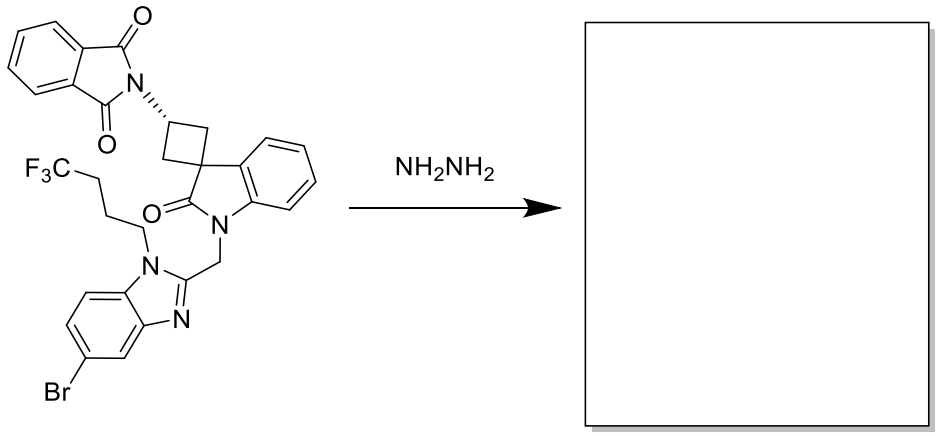

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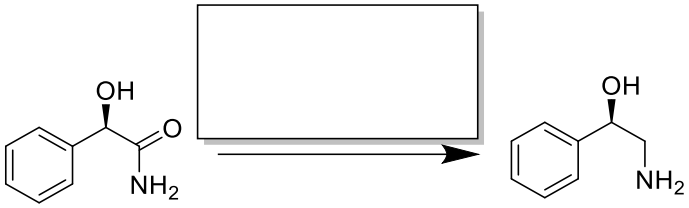

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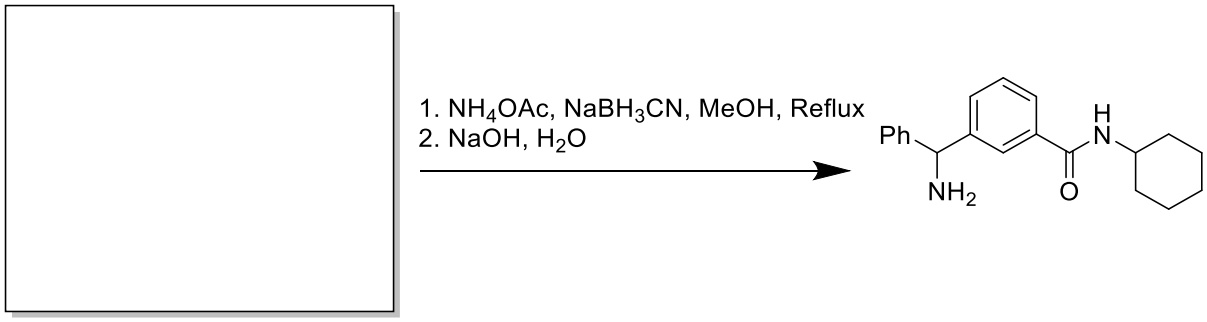

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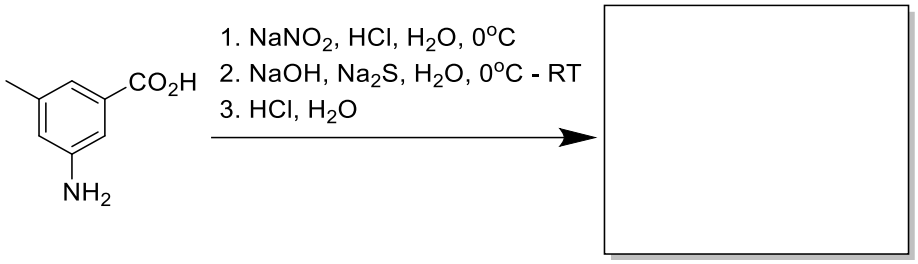

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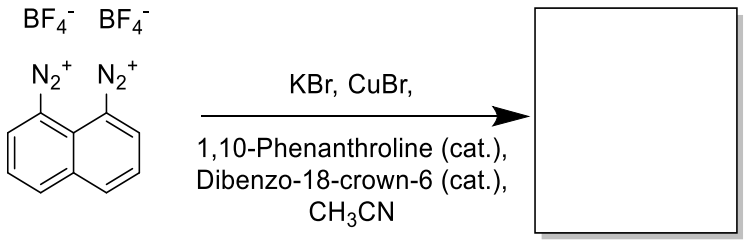

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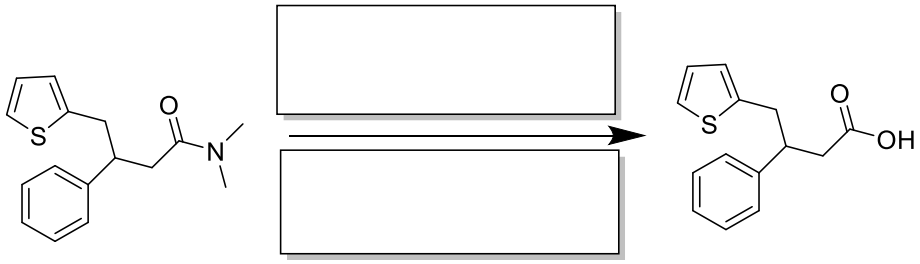

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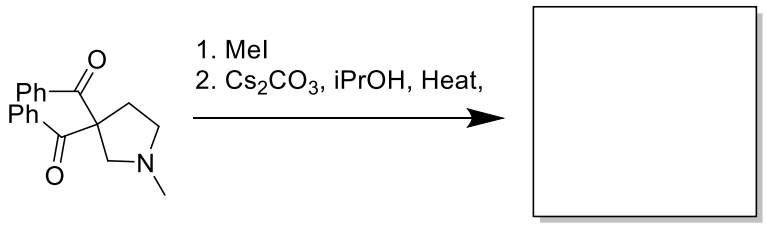

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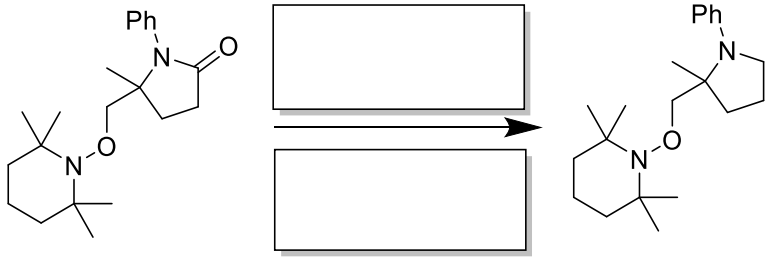

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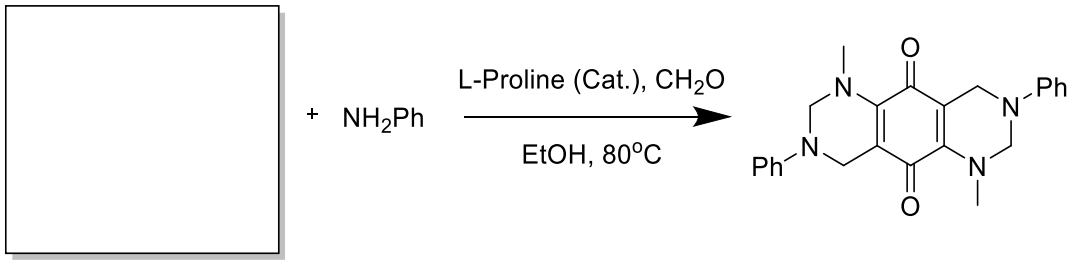

Note: The L-Proline catalyst is an acid catalyst.

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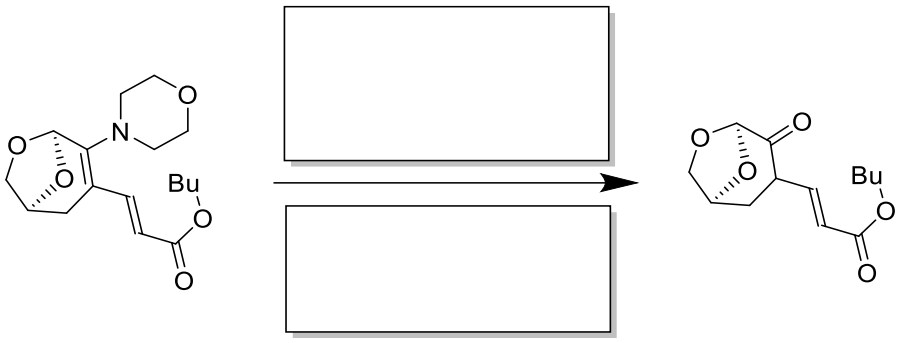

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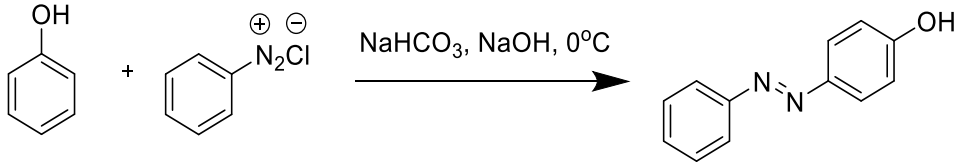
Section 12 – Mechanism Questions

Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

12.2.1



Miao, T.; Liu, M.; He, Z.; Zhang, G.; Xue, X.; Zhang, W. Donor-Acceptor Engineering Enables Kinetic Control of Chirality Transfer in Side Chain Polymers. *Angew. Chem. Int. Ed.* **2026**, *65* (12), e21913. https://doi.org/10.1002/anie.202521913

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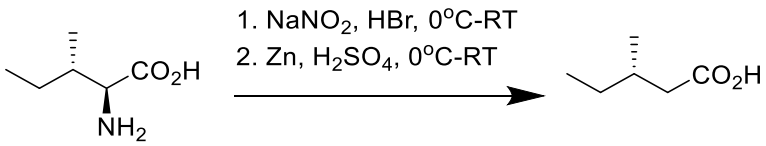
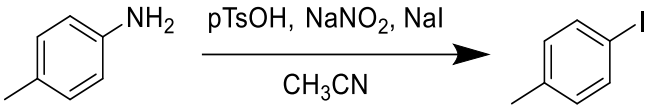


Kumaraswamy, G.; Markondaiah, B. Stereoselective Synthesis of Belactosin C and Its Derivatives Using a Catalytic Proline Catalyzed Crossed-Aldol Reaction. *Tetrahedron Lett.* **2007**, *48* (10), 1707-1709. https://doi.org/10.1016/j.tetlet.2007.01.059

12.2.3



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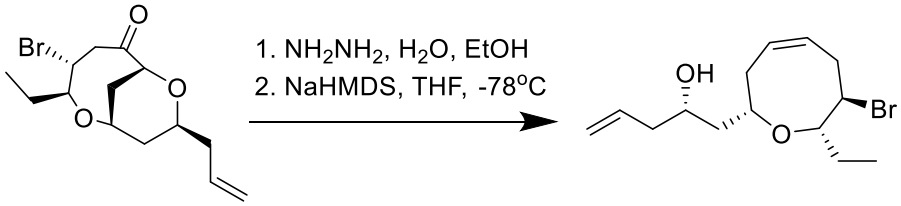

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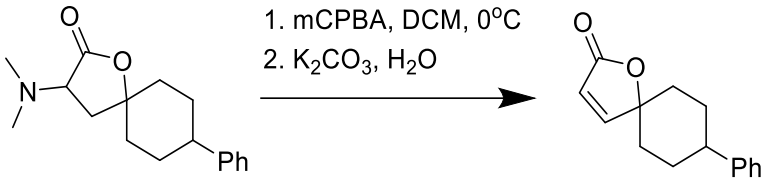

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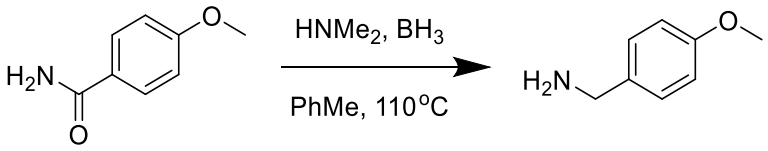

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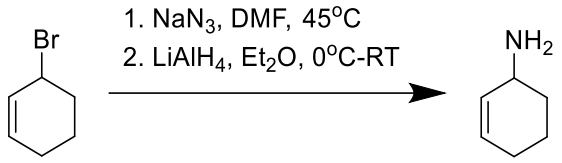

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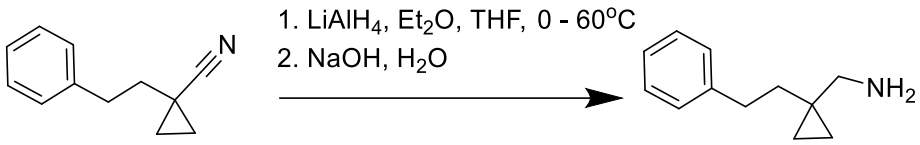

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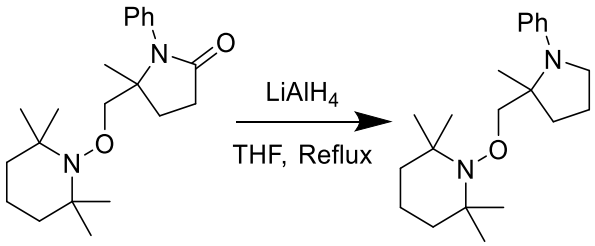
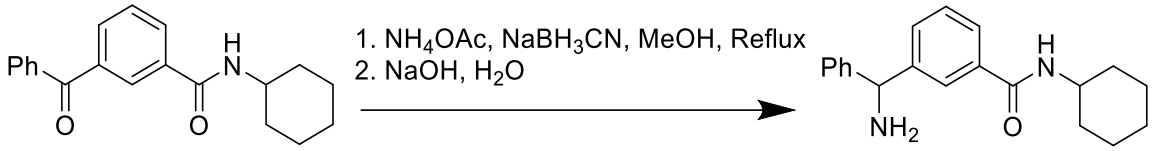


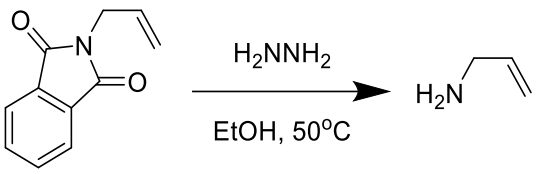
Suryawanshi, S. M.; Singh, M.; Samanta, R. C. Electrochemical Generation of *N*-Centered Radicals and Their Reactivity Toward Cyclization and Subsequent C−C Bond Cleavage. *Helv. Chim. Acta* **2026**, *109* (4), e00225. https://doi.org/10.1002/hlca.202500225

12.2.10



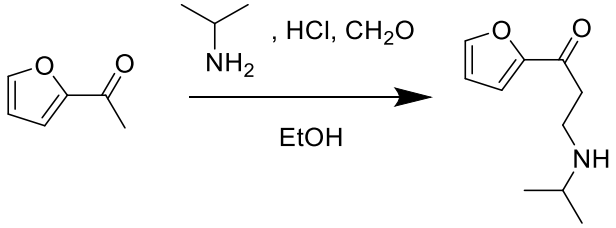
Trifonov, L.; Boshoff, H. I.; Roma, J. S. O.; Fan, Y.; Forbes, H. E.; Barry, C. E.; Oh, S. Structure-Activity Relationship Study of a New Class of 2-Amino-3,4-dihydroquinazolines as Antitubercular Agents. *Bioorg. Med. Chem.* **2026**, *134*, 118549. https://doi.org/10.1016/j.bmc.2026.118549

12.2.11



Huang, J.; Yan, X.; Liu, X.; Chen, Z.; Jiang, T.; Zhang, L.; Ju, G.; Huang, G.; Wang, C. Enantioselective Ni-Catalyzed 1,2-Borylalkynylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2024**, *146* (25), 17140-17149. https://doi.org/10.1021/jacs.4c03022

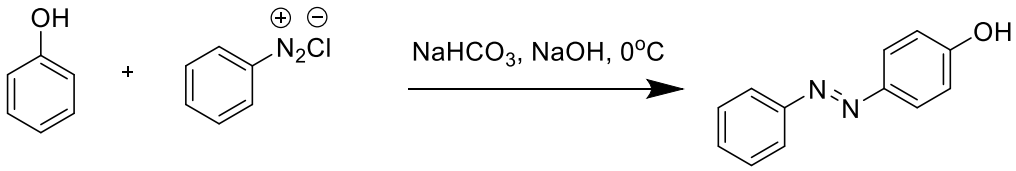
12.2.12



Note: Assume there was a basic workup following the reaction.

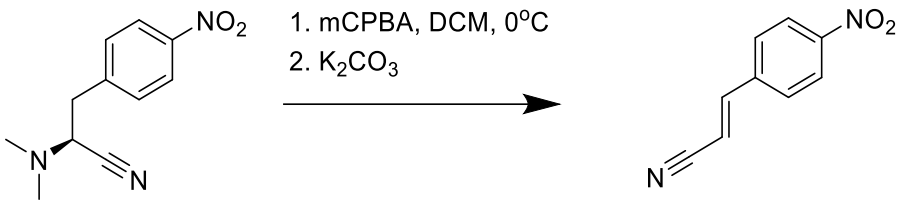
Lewis, D.; Zhang, Y.; Prisinzano, T.; Dersch, C. M.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. Further Exploration of 1-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}piperazine (GBR 12909): Role of N-Aromatic, N-Heteroaromatic, and 3-Oxygenated N-phenylpropyl Substituents on Affinity for the Dopamine and Serotonin Transporter. *Bioorg. Med. Chem. Lett.* **2003**, *13* (7), 1385–1389. https://doi.org/10.1016/S0960-894X(03)00108-2

12.2.13



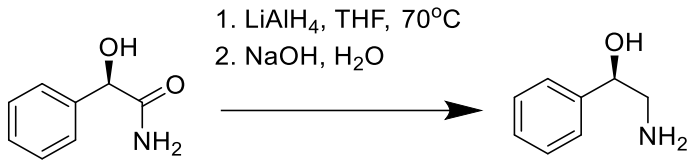
Miao, T.; Liu, M.; He, Z.; Zhang, G.; Xue, X.; Zhang, W. Donor-Acceptor Engineering Enables Kinetic Control of Chirality Transfer in Side Chain Polymers. *Angew. Chem. Int. Ed.* **2026**, *65* (12), e21913. https://doi.org/10.1002/anie.202521913

12.2.14



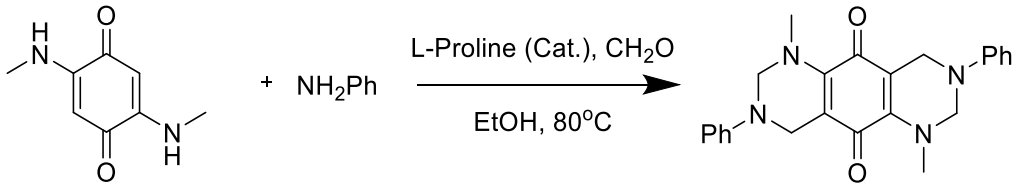
Kim, T. W.; Park, J.; Cheon, C.-H. Development of a Protocol for Synthesis of Nitrocinnamonitriles from Nitrotoluenes. *J. Org. Chem.* **2026**, *91* (18), 6243-6254. https://doi.org/10.1021/acs.joc.5c03178

12.2.15



Aubineau, T.; Dupas, A.; Zeng, T.; Cossy, J. Iron-Catalyzed Diastereoselective Synthesis of Disubstituted Morpholines via C–O or C–N Bond Formation. *Synlett* **2021**, *32* (5), 525-531. https://doi.org/10.1055/s-0040-1707902

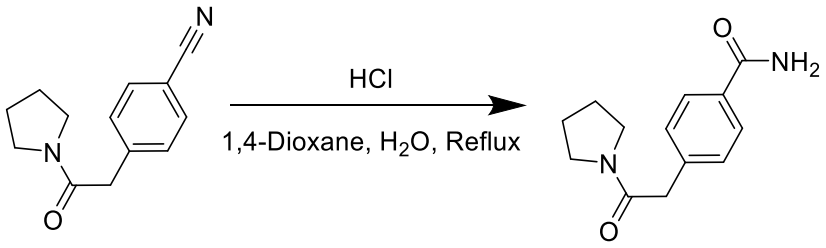
12.2.16



Note: The L-Proline catalyst is an acid catalyst.

Van Hoof, M.; Bynens, L.; Daelemans, B.; Rodríguez González, M. C.; Van Meervelt, L.; De Feyter, S.; Dehaen, W. Octahydropyrimido[4,5-g]quinazoline-5,10-diones: Their Multicomponent Synthesis, Self-Assembly on Graphite and Electrochemistry. *Chem. Commun*. **2022**, *58* (55), 7686–7689. https://doi.org/10.1039/D2CC02070J

12.2.17



Murugan, C.; Chindan, B.; Yogaraj, S. R.; Parakkal, S. C.; Balakrishnan, V.; Rasappan, R. Oxidative Hetero-Coupling: Iron- and Copper-Mediated 1,2-Dicarbofunctionalization. *J. Am. Chem. Soc.* **2026**, *148* (23), 23577-23584. https://doi.org/10.1021/jacs.5c21411

Section 13: Pericyclic Reactions

Required foundation for this section:

Cycloaddition reaction (*e.g.*, Diels-Alder)

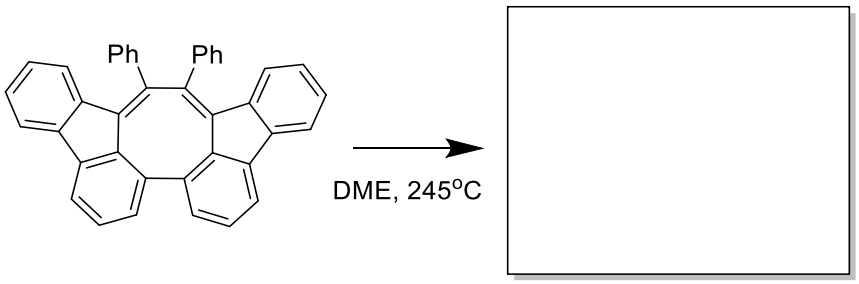
Electrocyclic reaction

Sigmatropic rearrangement (*e.g.*, Claisen rearrangement, Cope rearrangement)

Section 13 – Box-Type Questions

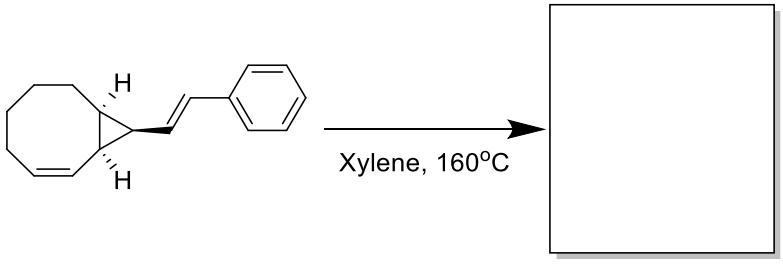
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

13.1.1



Chen, H.-H.; Liu, C.-H.; Ou, W.-T.; Huang, K.-H.; Yang, C.-J.; Cheng, M.-J.; Wu, Y.-T. 1,8-Di(2-ethynylaryl)biphenylenes: Palladium-Catalyzed Intramolecular Cycloisomerization and Subsequent Thermal Rearrangement. *Org. Lett.* **2025**, *27* (46), 12886-12891. https://doi.org/10.1021/acs.orglett.5c04302

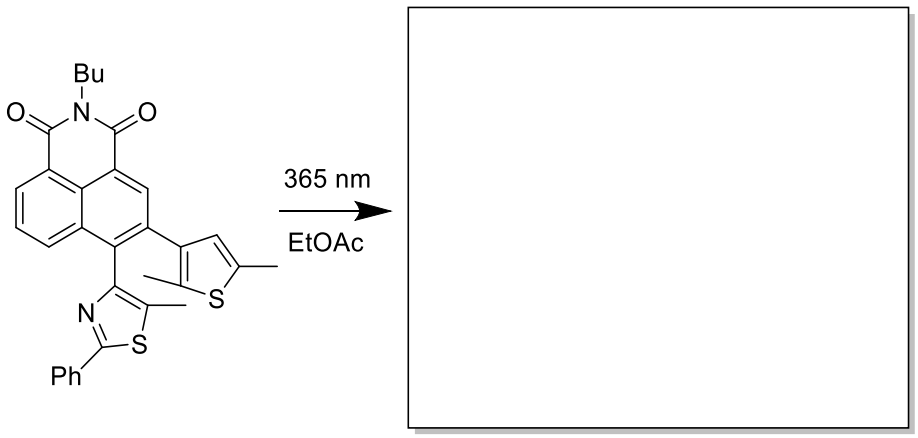
13.1.2



Hint: A bicyclic product is made.

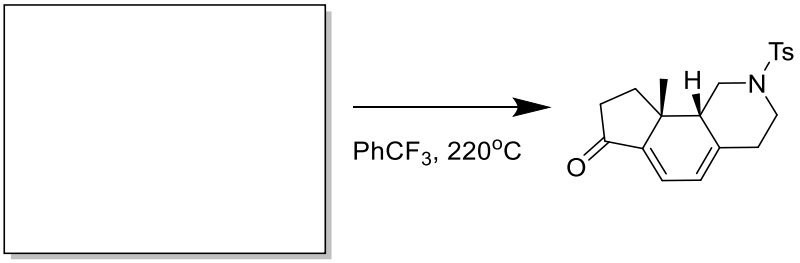
Fang, Z.; Ma, Y.; Liu, S.; Bai, H.; Li, S.; Ning, Y.; Zanoni, G.; Liu, Z. Silver-Catalyzed [4 + 3] Cycloaddition of 1,3-Dienes with Alkenyl-*N*-Triftosylhydrazones: A Practical Approach to 1,4-Cycloheptadienes. *Org. Chem. Front.* **2022**, *9* (16), 4426-4434. https://doi.org/10.1039/D2QO00806H

13.1.3



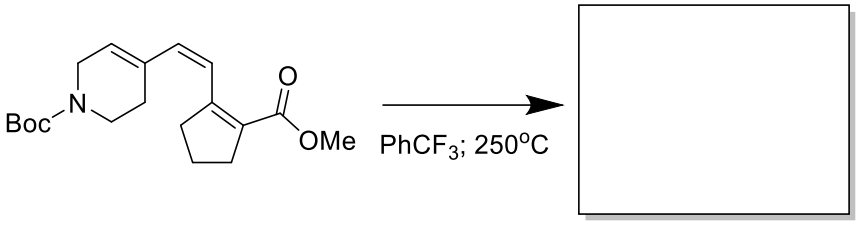
Orhan, E.; Köse, M.; Yazan, T. The Synthesis of New 3,4-(Bisaryl)-1,8-naphthalimide and 2,3-(Bisaryl)-7*H*-benzimidazo[2,1-*a*]benzo[*d*]isoquinolin-7-one Compounds and an Investigation of Their Photochromic Properties. *Turk. J. Chem.* **2018**, *42* (4), 1086-1094. https://doi.org/10.3906/kim-1711-3

13.1.4



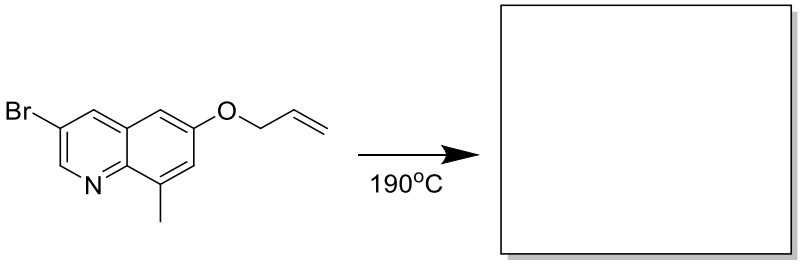
Krieger, J.-P.; Ricci, G.; Lesuisse, D.; Meyer, C.; Cossy, J. Efficient and Modular Synthesis of New Structurally Diverse Functionalized [*n*]Paracyclophanes by a Ring-Distortion Strategy. *Angew. Chem. Int. Ed.* **2014**, *53* (33), 8705-8708. https://doi.org/10.1002/anie.201401070

13.1.5



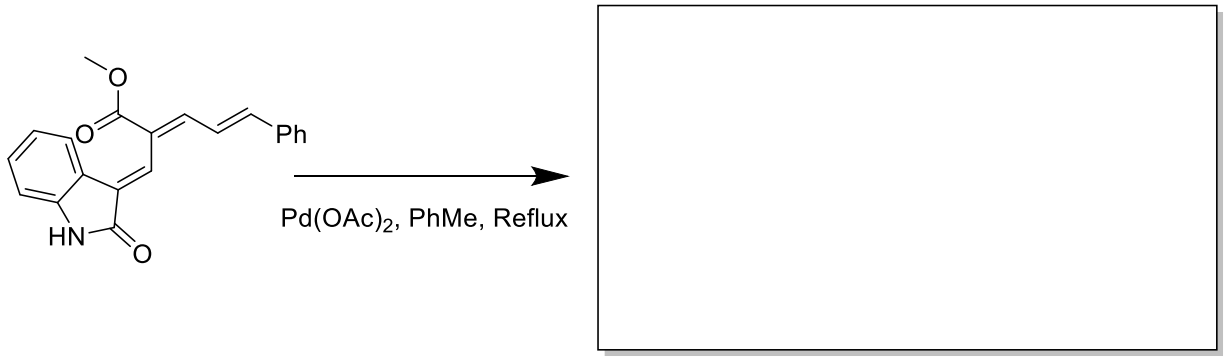
Krieger, J.-P.; Ricci, G.; Lesuisse, D.; Meyer, C.; Cossy, J. Efficient and Modular Synthesis of New Structurally Diverse Functionalized [*n*]Paracyclophanes by a Ring-Distortion Strategy. *Angew. Chem. Int. Ed.* **2014**, *53* (33), 8705-8708. https://doi.org/10.1002/anie.201401070

13.1.6



Murphy Kessabi, F.; Beaudegnies, R.; Quaranta, L.; Lamberth, C. Synthesis of Conformationally Locked Analogs of Quinolin-6-yloxyacetamide Fungicides. *Tetrahedron Lett.* **2016**, *57* (49), 5511-5513. https://doi.org/10.1016/j.tetlet.2016.10.104

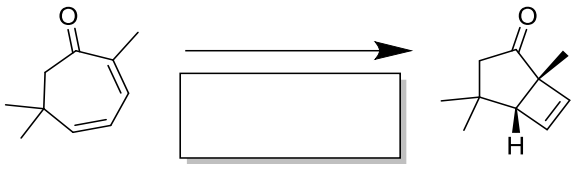
13.1.7



Note: Learners in introductory organic chemistry do not need to understand the catalytic role of $Pd(OAc)_2$ in this reaction.

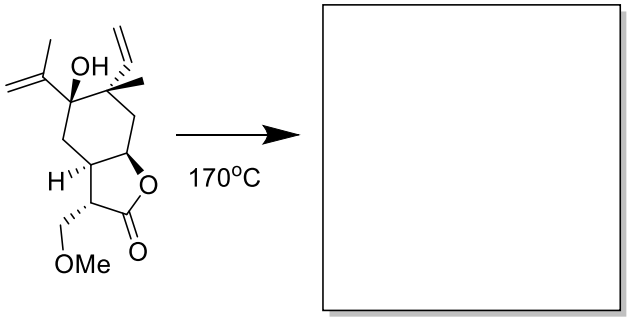
Kim, K. H.; Moon, H. R.; Lee, J.; Kim, J.; Kim, J. N. Diastereoselective Synthesis of Six-Membered Carbocyclic Spirooxindoles via 6π-Electrocyclization of 3-Dienylidene-2-oxindoles. *Adv. Synth. Catal.* **2015**, *357* (7), 1532-1544. https://doi.org/10.1002/adsc.201500260

13.1.8



Holl, M. G.; Lambert, T. H. Ring-Opening Carbonyl-Olefin Metathesis of Cyclobutenes. *ACS Catal.* **2022**, *12* (9), 4813-4817. https://doi.org/10.1021/acscatal.2c01188

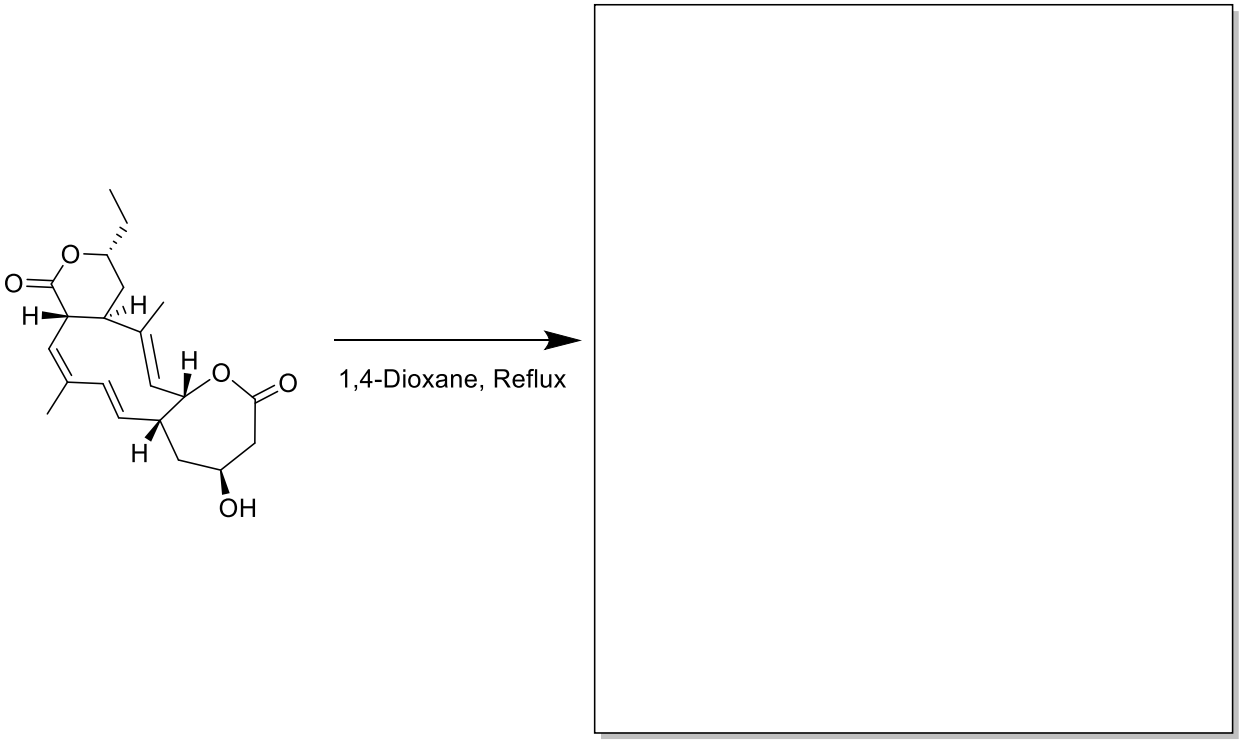
13.1.9



Hint: There is an oxy-Cope rearrangement followed by the formation of a five and seven-membered ring.

Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* **2024**, *26* (22), 4648-4653. https://doi.org/10.1021/acs.orglett.4c01374

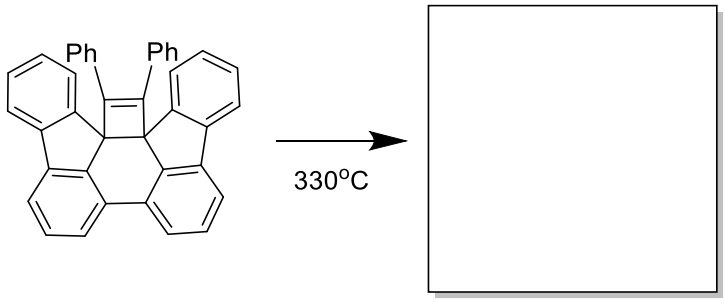
13.1.10



Hint: Three products are made, propose structures for all three products.

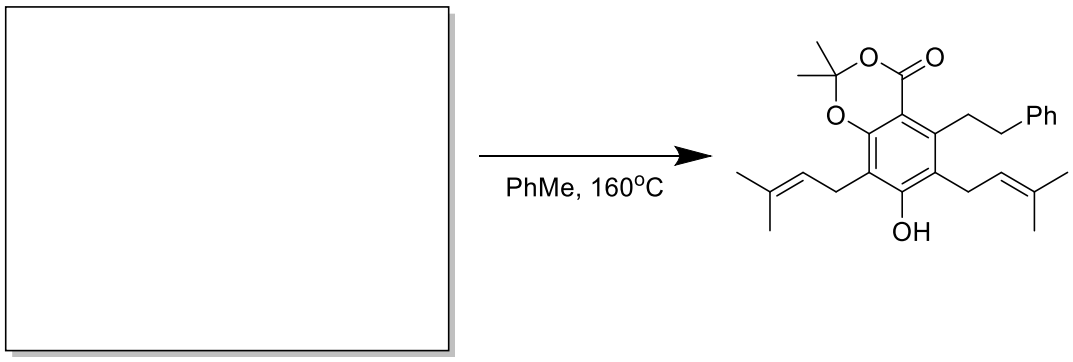
Decker, R. L.; Schray, D.; Pfeffer, H. I.; Grond, S.; Wagner, J. P. Conformations and Rearrangements of Collinolactone: Experiments and Theory on a Dynamic Cyclodecatriene. *Chem. Eur. J.* **2024**, *30* (10), e202303435. https://doi.org/10.1002/chem.202303435

13.1.11



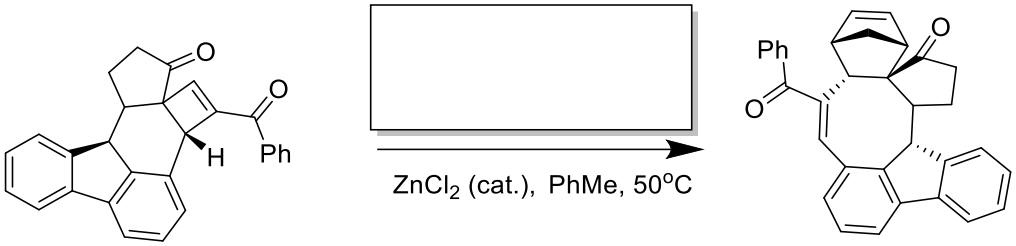
Chen, H.-H.; Liu, C.-H.; Ou, W.-T.; Huang, K.-H.; Yang, C.-J.; Cheng, M.-J.; Wu, Y.-T. 1,8-Di(2-ethynylaryl)biphenylenes: Palladium-Catalyzed Intramolecular Cycloisomerization and Subsequent Thermal Rearrangement. *Org. Lett.* **2025**, *27* (46), 12886-12891. https://doi.org/10.1021/acs.orglett.5c04302

13.1.12



Patel, C.; Mies, T.; White, A. J. P.; Parsons, P. J.; Barrett, A. G. M. Biomimetic Syntheses of Amorfrutin C and C-5 Substituted Amorfrutin Analogues. *Eur. J. Org. Chem.* **2021**, *2021* (8), 1258-1265. https://doi.org/10.1002/ejoc.202001487

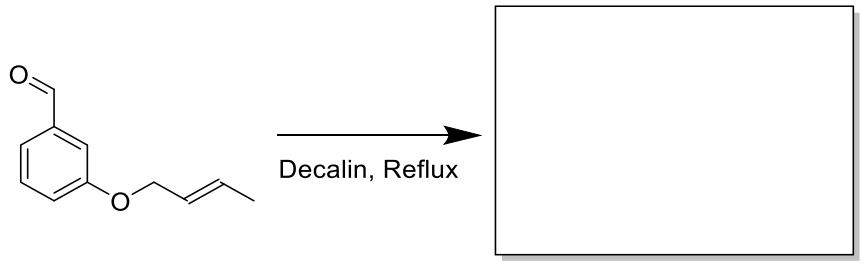
13.1.13



Hint: An intramolecular reaction occurs before the reaction with a reagent.

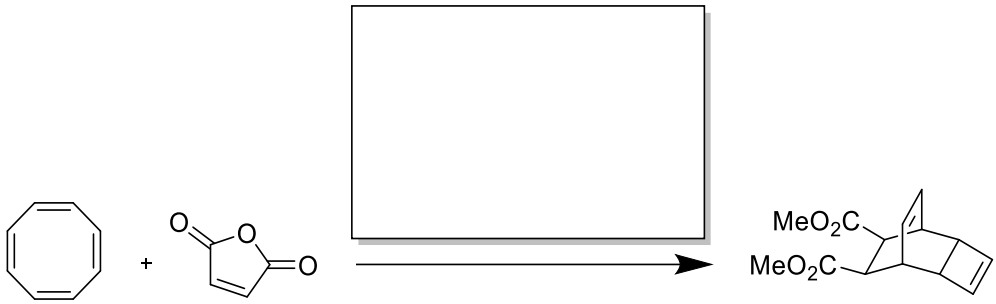
Corti, V.; Barløse, C. L.; Østergaard, N. L.; Kristensen, A.; Jessen, N. I.; Jørgensen, K. A. Organocatalytic Enantioselective Thermal [4 + 4] Cycloadditions. *J. Am. Chem. Soc.* **2023**, *145* (2), 1448-1459. https://doi.org/10.1021/jacs.2c12750

13.1.14



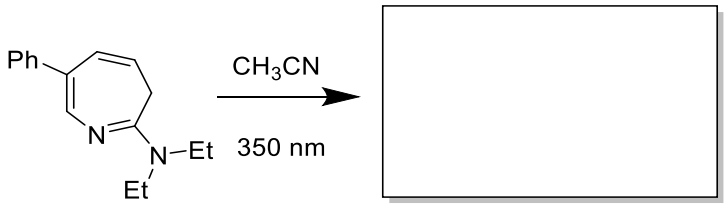
Chang, M.-Y.; Lai, K.-X.; Chen, K.-T. *tert*-BuOOH/Cu(acac)$_2$-Mediated Intramolecular Oxidative Lactonization of *o*-Allyl Arylaldehydes: Synthesis of 1-Oxoisochromans. *Synthesis* **2021**, *53* (3), 527-537. https://doi.org/10.1055/s-0040-1706469

13.1.15



Holl, M. G.; Lambert, T. H. Ring-Opening Carbonyl-Olefin Metathesis of Cyclobutenes. *ACS Catal.* **2022**, *12* (9), 4813-4817. https://doi.org/10.1021/acscatal.2c01188

13.1.16



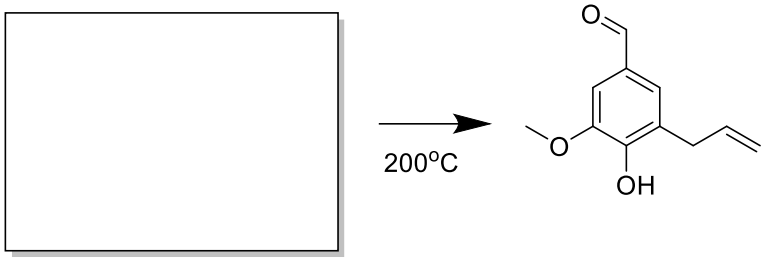
Matador, E.; Tilby, M. J.; Saridakis, I.; Pedrón, M.; Tomczak, D.; Llaveria, J.; Atodiresei, I.; Merino, P.; Ruffoni, A.; Leonori, D. A Photochemical Strategy for the Conversion of Nitroarenes into Rigidified Pyrrolidine Analogues. *J. Am. Chem. Soc.* **2023**, *145* (50), 27810-27820. https://doi.org/10.1021/jacs.3c10863

13.1.17



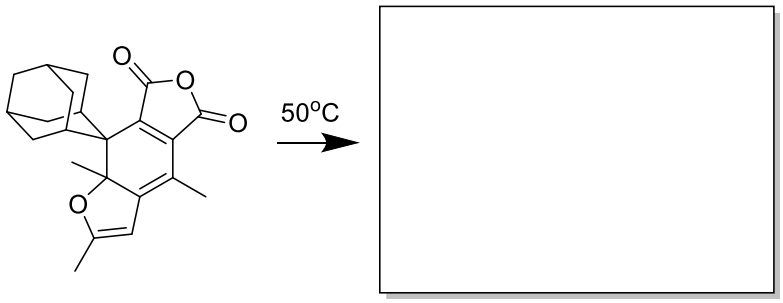
Luo, Y.; Zhou, L.; Qi, X.; Min, C. Divergent Skeletal Editing of Pyridinium Salts to Azepinones and Pyrrolidinones via Formal Carbonyl Insertion. *J. Am. Chem. Soc.* **2026**, *148* (18). https://doi.org/10.1021/jacs.6c03052

13.1.18



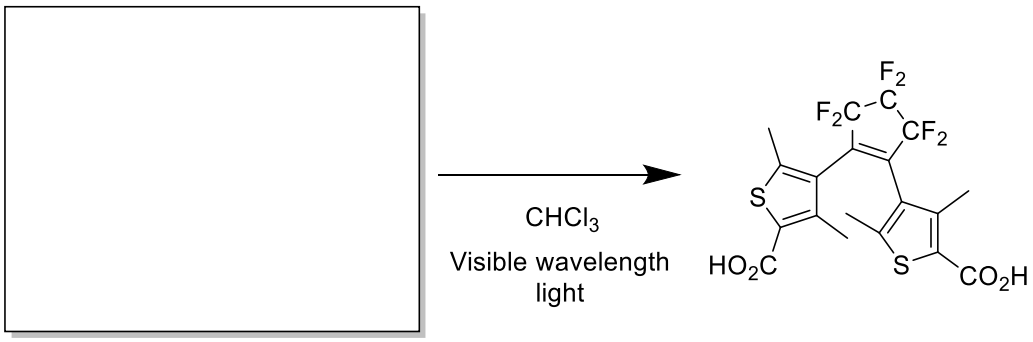
Gao, Z.; Chen, Q.; Xie, H. Atom-Economic Molecular Design of Vanillin-Based Tetraene for Tunable Polyesters via Thiol-Ene Click Polymerization. *Chem. Commun.* **2026**, *62* (29), 7603-7606. https://doi.org/10.1039/D6CC00908E

13.1.19



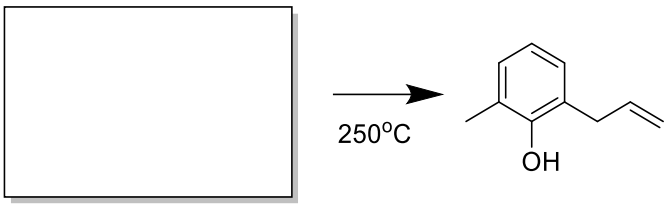
Eichler, C.; Rázková, A.; Müller, F.; Kopacka, H.; Huppertz, H.; Hofer, T. S.; Schwartz, H. A. Paving the Way to the First Functional Fulgide@MOF Hybrid Materials. *Chem. Mater.* **2021**, *33* (10), 3757-3766. https://doi.org/10.1021/acs.chemmater.1c00873

13.1.20



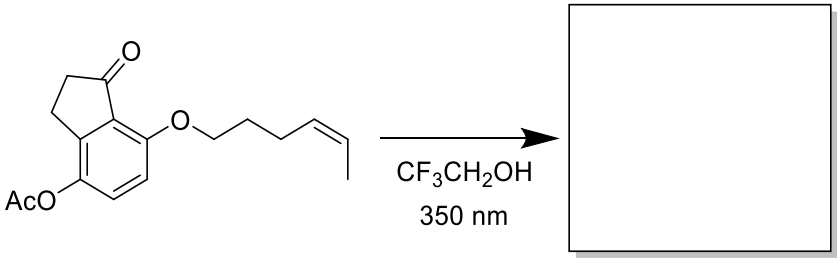
Saeki, Y.; Kayanuma, M.; Nitta, A.; Shigeta, Y.; Kawamura, I.; Nakagawa, T.; Ubukata, T.; Yokoyama, Y. On-Demand Chirality Transfer of Human Serum Albumin to Bis(thiophen-2-yl)hexafluorocyclopentenes through Their Photochromic Ring Closure. *J. Org. Chem.* **2021**, *86* (18), 12549-12558. https://doi.org/10.1021/acs.joc.1c00849

13.1.21



Nagafuchi, M.; Mizumachi, T.; Sato, Y.; Takatsuki, M.; Matsuzaki, T.; Suzuki, T.; Nakayama, A.; Sako, M.; Arisawa, M. Long-Range Isomerisation/Cyclopropane Isomerisation/Cycloisomerisation/Aromatisation Reactions Using Multifunctional Rhodium Catalysts. *Org. Biomol. Chem.* **2026**, *24* (22), 4605-4614. https://doi.org/10.1039/D6OB00534A

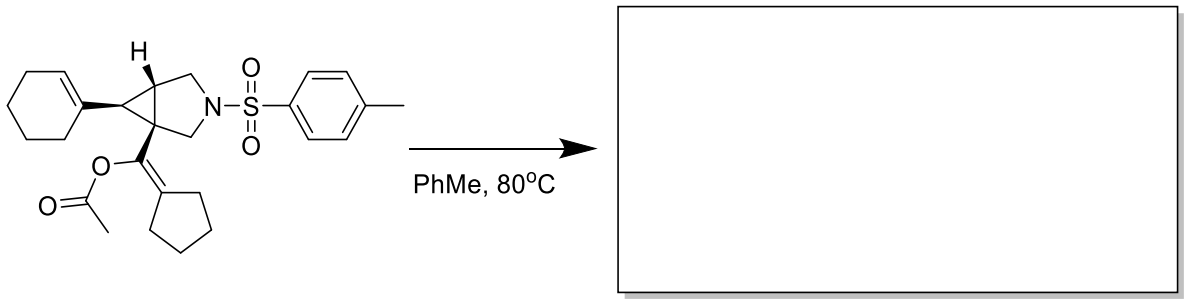
13.1.22



Hint: A four-membered ring is formed.

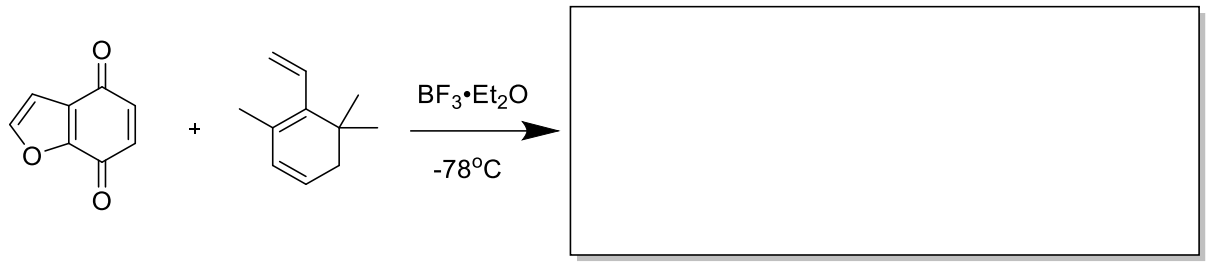
Gilbert, A.; Zuber, J.; Bach, T. Intramolecular *ortho* Photocycloaddition of 4-Substituted 7-(4′-Alkenyloxy)-1-indanones and Ensuing Reaction Cascades. *J. Org. Chem.* **2025**, *90* (11), 4099-4107. https://doi.org/10.1021/acs.joc.5c00171

13.1.23



Rao, W.; Sally; Berry, S. N.; Chan, P. W. H. Gold-Catalyzed Cycloisomerization of 1,6,8-Dienyne Carbonates and Esters to *cis*-Cyclohepta-4,8-diene-Fused Pyrrolidines. *Chem. Eur. J.* **2014**, *20* (41), 13174-13180. https://doi.org/10.1002/chem.201402500

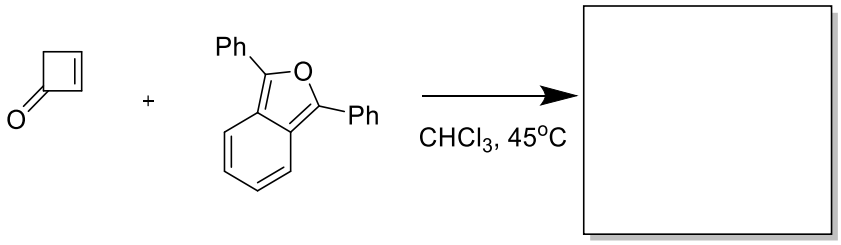
13.1.24



Note: $BF_3•Et_2O$ is a Lewis acid catalyst used to help favor the production of a particular product. Only two regioisomers are shown in the answer while their stereoisomers are omitted.

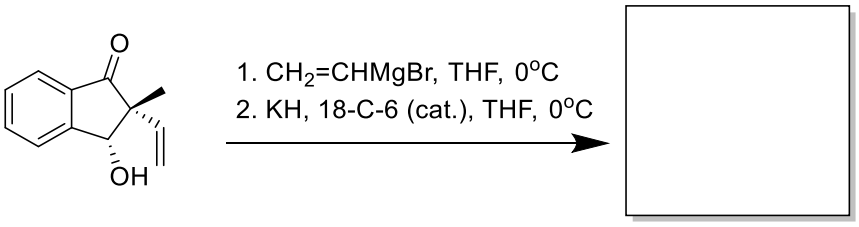
Papidocha, S. M.; Bulthaupt, H. H.; Carreira, E. M. Synthesis of Neocaesalpin A, AA, and Nominal Neocaesalpin K**. *Angew Chem Int Ed* **2023**, *62* (48), e202310149. https://doi.org/10.1002/anie.202310149

13.1.25



Li, X.; Danishefsky, S. J. Cyclobutenone as a Highly Reactive Dienophile: Expanding Upon Diels-Alder Paradigms. *J. Am. Chem. Soc.* **2010**, *132* (32), 11004-11005. https://doi.org/10.1021/ja1056888

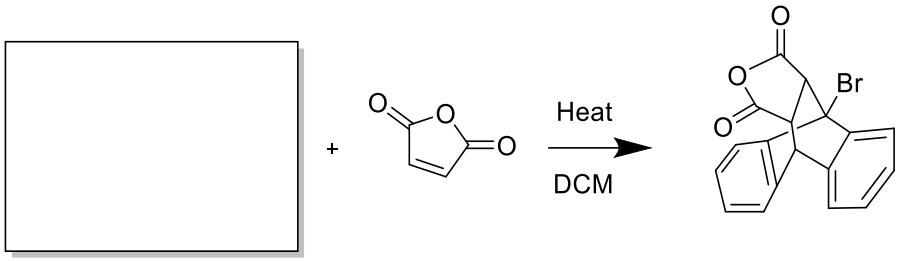
13.1.26



Hint: A nine-membered ring is formed. Learners in introductory organic chemistry can ignore the catalytic role of 18-C-6.

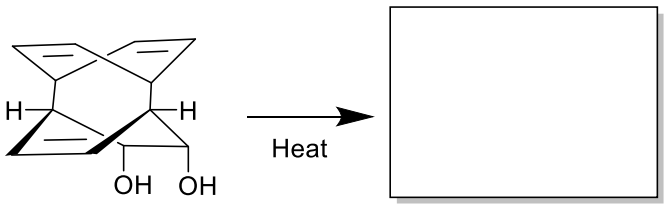
Mondal, A.; Satpathi, B.; Ramasastry, S. S. V. Phosphine-Catalyzed Intramolecular Vinylogous Aldol Reaction of α-Substituted Enones. *Org. Lett.* **2022**, *24* (1), 256-261. https://doi.org/10.1021/acs.orglett.1c03913

13.1.27



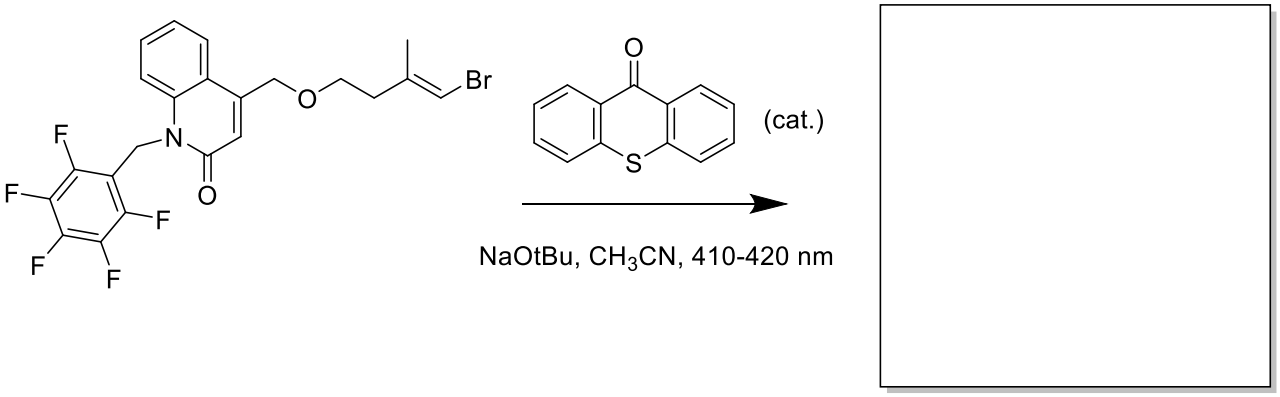
Jadwiszczak, M. J.; Leszczyński, P. J.; Malinowski, P. J. The Role of $AlCl_3$ in Catalysis and Regioselectivity in Diels-Alder Reactions Between Polycyclic Aromatic Hydrocarbons and Maleimides. *Eur. J. Org. Chem.* **2026**, *29* (16), e202501136. https://doi.org/10.1002/ejoc.202501136

13.1.28



Gan, H.; Horner, M. G.; Hrnjez, B. J.; McCormack, T. A.; King, J. L.; Gasyna, Z.; Chen, G.; Gleiter, R.; Yang, N.-C. C. Chemistry of *syn-o,o'*-Dibenzene. *J. Am. Chem. Soc.* **2000**, *122*, 12098-12111. https://doi.org/10.1021/ja0023579

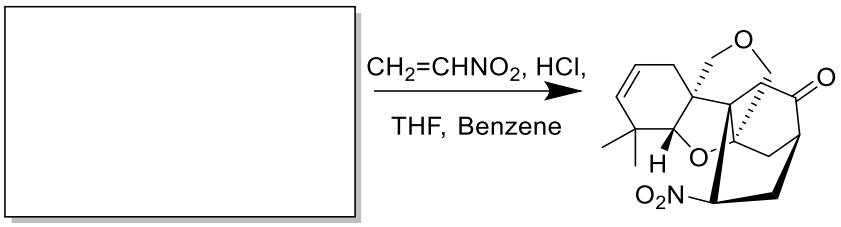
13.1.29



Hint: From the reaction conditions, note that the transformation is performed under basic, photochemical conditions. Learners in introductory organic chemistry do not need to understand the catalytic role of the catalyst in this reaction. The reaction forms a new six-membered ring.

Pan, G.; Qin, S.; Xu, D.; Kühn, F. E.; Guo, H. Visible Light-Induced Pericyclic Cascade Reaction for the Synthesis of Quinolinone Derivatives with an Oxabicyclo[4.2.0]octene Skeleton. *Org. Lett.* **2021**, *23* (8), 2959-2963. https://doi.org/10.1021/acs.orglett.1c00642

13.1.30

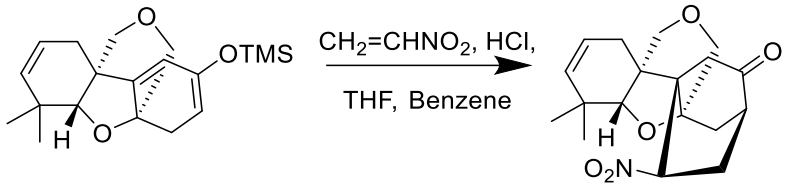


Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. Enantioselective Total Synthesis of (−)-Maoecrystal V. *J. Am. Chem. Soc.* **2014**, *136* (51), 17750-17756. https://doi.org/10.1021/ja5109694

Section 13 – Mechanism Questions

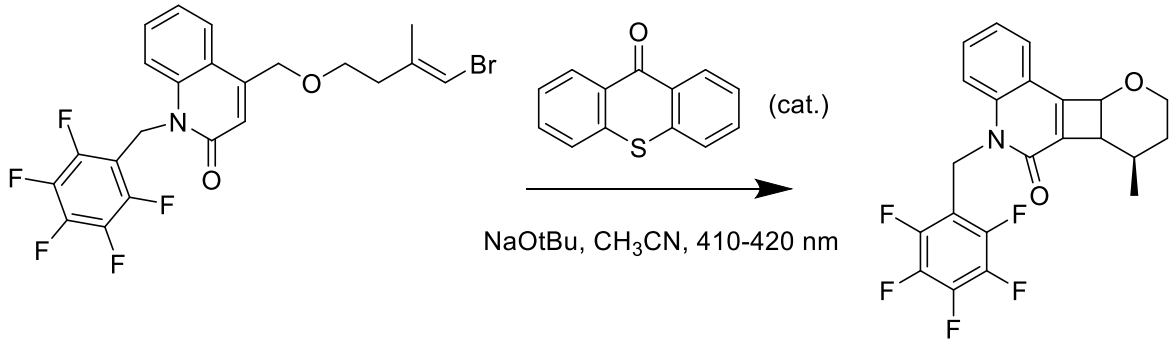
Draw the reaction mechanism for each reaction shown. Use curved arrows to illustrate how the reactants are converted into the product using the reagents provided. Only the product shown is of interest, even if additional products or byproducts may be formed. Questions are drawn from material covered in the section and may be based on complex molecules from the chemical literature.

13.2.1



Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. Enantioselective Total Synthesis of (−)-Maoecrystal V. *J. Am. Chem. Soc.* **2014**, *136* (51), 17750-17756. https://doi.org/10.1021/ja5109694

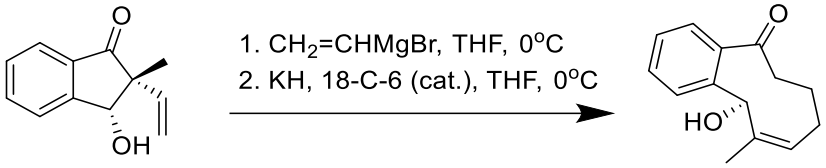
13.2.2



Hint: From the reaction conditions, note that the transformation is performed under basic, photochemical conditions. Learners in introductory organic chemistry do not need to understand the catalytic role of the catalyst in this reaction.

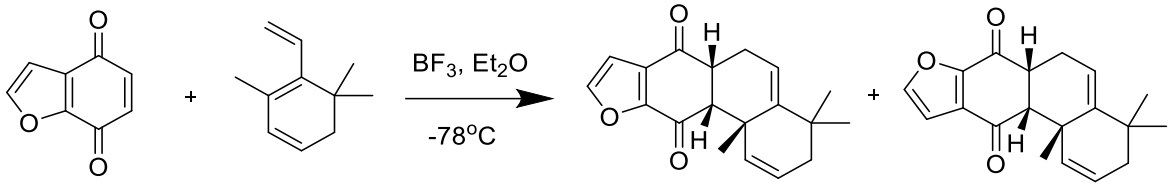
Pan, G.; Qin, S.; Xu, D.; Kühn, F. E.; Guo, H. Visible Light-Induced Pericyclic Cascade Reaction for the Synthesis of Quinolinone Derivatives with an Oxabicyclo[4.2.0]octene Skeleton. *Org. Lett.* **2021**, *23* (8), 2959-2963. https://doi.org/10.1021/acs.orglett.1c00642

13.2.3



Mondal, A.; Satpathi, B.; Ramasastry, S. S. V. Phosphine-Catalyzed Intramolecular Vinylogous Aldol Reaction of α-Substituted Enones. *Org. Lett.* **2022**, *24* (1), 256-261. https://doi.org/10.1021/acs.orglett.1c03913

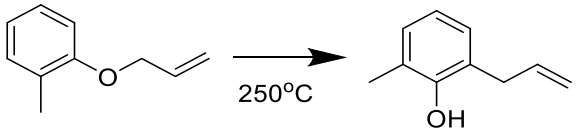
13.2.4



Note: BF_3, Et_2O is a Lewis acid catalyst used to help favor the production of a particular product. For an introductory organic chemistry course, it does not have to be incorporated in the reaction mechanism.

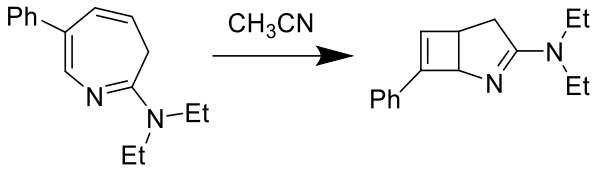
Papidocha, S. M.; Bulthaupt, H. H.; Carreira, E. M. Synthesis of Neocaesalpin A, AA, and Nominal Neocaesalpin K**. *Angew Chem Int Ed* **2023**, *62* (48), e202310149. https://doi.org/10.1002/anie.202310149

13.2.5



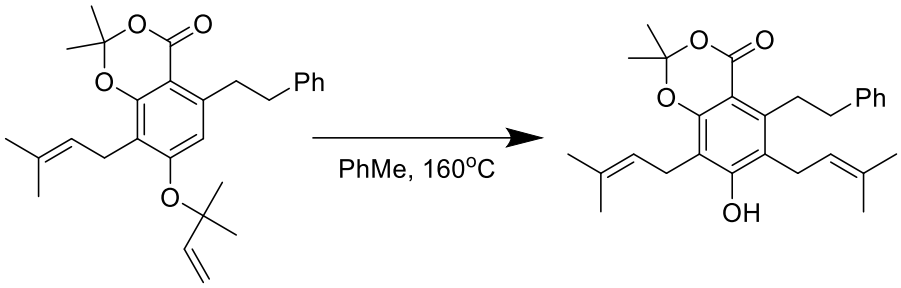
Nagafuchi, M.; Mizumachi, T.; Sato, Y.; Takatsuki, M.; Matsuzaki, T.; Suzuki, T.; Nakayama, A.; Sako, M.; Arisawa, M. Long-Range Isomerisation/Cyclopropane Isomerisation/Cycloisomerisation/Aromatisation Reactions Using Multifunctional Rhodium Catalysts. *Org. Biomol. Chem.* **2026**, *24* (22), 4605-4614. https://doi.org/10.1039/D6OB00534A

13.2.6



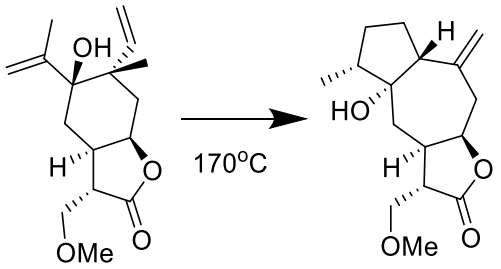
Matador, E.; Tilby, M. J.; Saridakis, I.; Pedrón, M.; Tomczak, D.; Llaveria, J.; Atodiresei, I.; Merino, P.; Ruffoni, A.; Leonori, D. A Photochemical Strategy for the Conversion of Nitroarenes into Rigidified Pyrrolidine Analogues. *J. Am. Chem. Soc.* **2023**, *145* (50), 27810-27820. https://doi.org/10.1021/jacs.3c10863

13.2.7



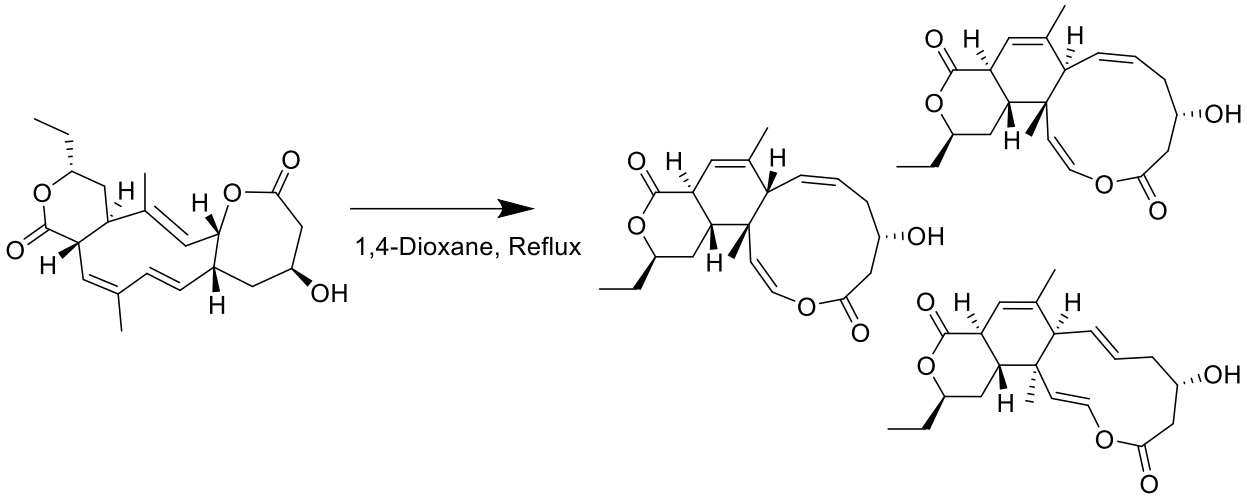
Patel, C.; Mies, T.; White, A. J. P.; Parsons, P. J.; Barrett, A. G. M. Biomimetic Syntheses of Amorfrutin C and C-5 Substituted Amorfrutin Analogues. *Eur. J. Org. Chem.* **2021**, *2021* (8), 1258-1265. https://doi.org/10.1002/ejoc.202001487

13.2.8



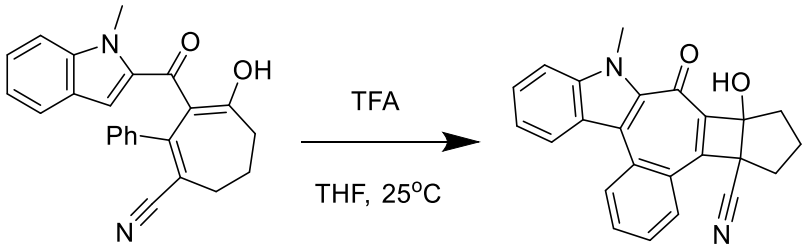
Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* **2024**, *26* (22), 4648-4653. https://doi.org/10.1021/acs.orglett.4c01374

13.2.9



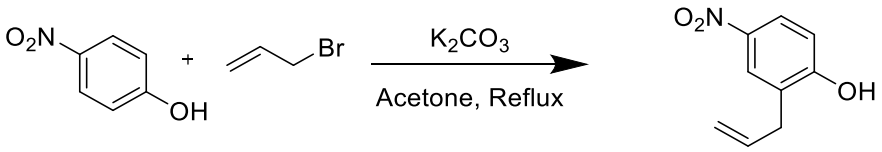
Decker, R. L.; Schray, D.; Pfeffer, H. I.; Grond, S.; Wagner, J. P. Conformations and Rearrangements of Collinolactone: Experiments and Theory on a Dynamic Cyclodecatriene. *Chem. Eur. J.* **2024**, *30* (10), e202303435. https://doi.org/10.1002/chem.202303435

13.2.10



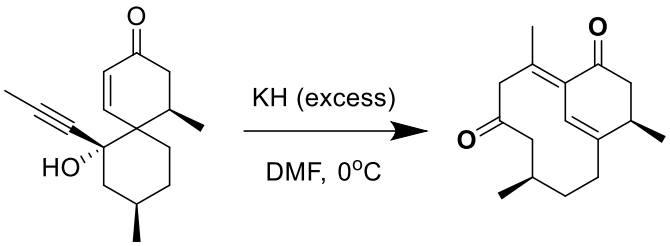
Wang, Z.; Liu, Y.; Liang, C.; Yan, Y.; Yang, L.; Wang, Y.; Jiang, Y.; Wang, C.; Li, Y. Visible Light Induced 6π Electrocyclization: Divergent Synthesis of Seven Membered Ring Derivatives. *Green Chem.* **2026**, *28* (17), 7286-7292. https://doi.org/10.1039/D6GC01010E

13.2.11



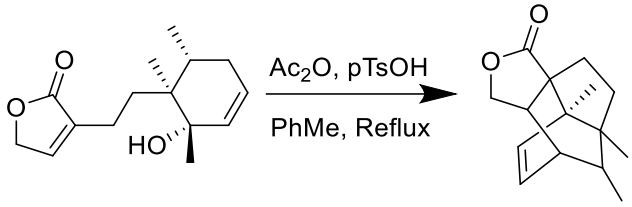
Majumdar, K. C.; Nandi, R. K.; Ganai, S. Synthesis of Phosphorus Containing Medium Ring Heterocycles by Sequential Claisen Rearrangement and Ring Closing Metathesis. *Tetrahedron Lett.* **2014**, *55* (6), 1247–1250. https://doi.org/10.1016/j.tetlet.2014.01.008

13.2.12



Ramella, V.; Roosen, P. C.; Vanderwal, C. D. Concise Formal Synthesis of the Pseudopterosins via Anionic Oxy-Cope/Transannular Michael Addition Cascade. *Org. Lett*. **2020**, *22* (8), 2883–2886. https://doi.org/10.1021/acs.orglett.0c00486

13.2.13



Hint: Esterification, Elimination, Diels-Alder

Kamo, S.; Kurosawa, H.; Matsuzawa, A.; Sugita, K. Total Synthesis of (−)-Lamellodysidine A via an Intramolecular Diels–Alder Reaction. *Org. Lett*. **2022**, *24* (3), 921–923. https://doi.org/10.1021/acs.orglett.1c04289

13.2.14



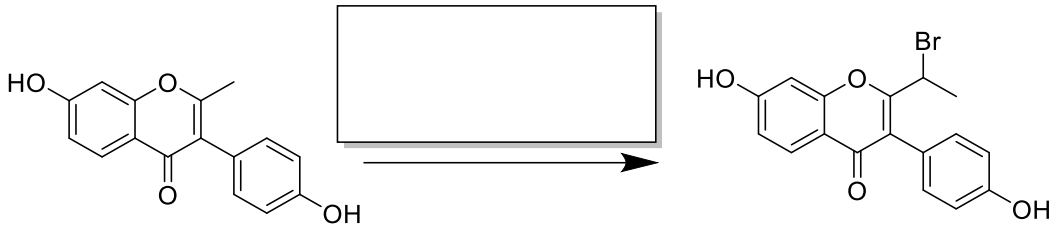
Rationalize the formation of all stereocenters in the product.

Zech, A.; Jandl, C.; Bach, T. Concise Access to the Skeleton of Protoilludane Sesquiterpenes through a Photochemical Reaction Cascade: Total Synthesis of Atlanticone C. *Angew. Chem. Int. Ed*. **2019**, *58*, 14629–14632. https://doi.org/10.1002/anie.201908619

Section 14: Multistep Synthesis 2

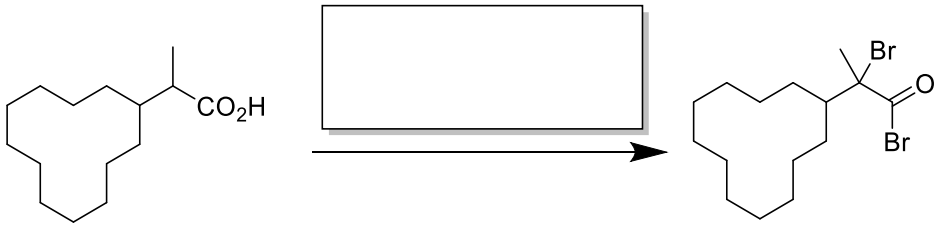
The multistep syntheses presented in this section draw upon fundamental concepts and reactions in all sections. For each of the questions below, provide reagents that would produce the product indicated from the starting material.

14.1



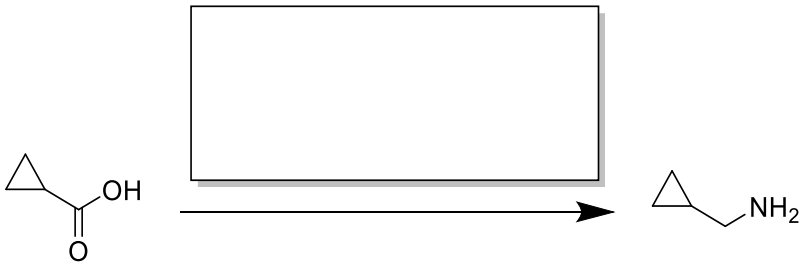
Al-Maharik, N.; Daqqa, M.; AlObaid, A.; Abdallah, L.; Zarrouk, A.; AlAli, A.; Warad, I. Synthesis, XRD/HSA-Interactions, Synthon, TD-DFT/Optical Analysis, Docking and Antibacterial Evaluation of Two (±)-Isoflavonoid Derivatives. *J. Mol. Struct.* **2024**, *1313*, 138700. https://doi.org/10.1016/j.molstruc.2024.138700

14.2



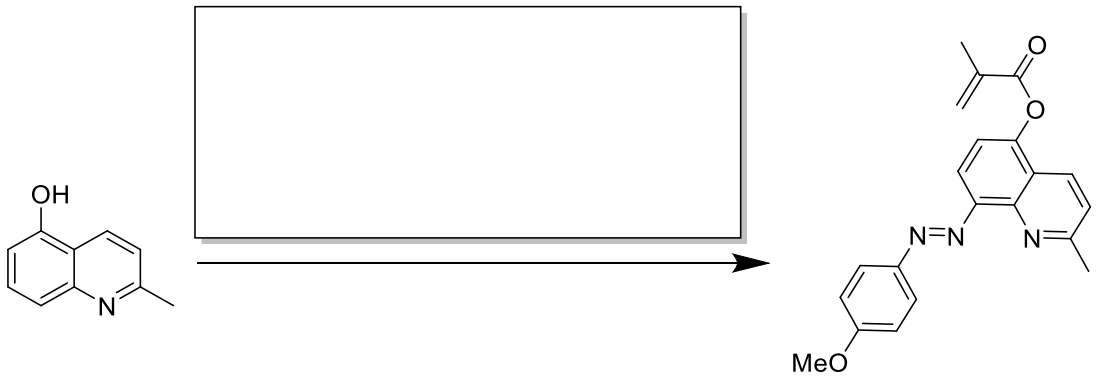
Zhong, F.; Anderson, R. L.; Oyala, P. H.; Fu, G. C. Photoinduced, Copper-Catalyzed Enantioconvergent Azidation of Alkyl Halides. *J. Am. Chem. Soc.* **2025**, *147* (36), 32963–32970. https://doi.org/10.1021/jacs.5c10003

14.3



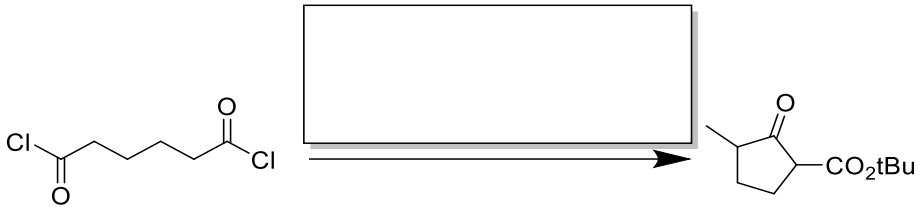
Qi, J.; Wang, C.; Wang, G.; O'Neill, P.; Reddy Dubbaka, S.; Ting Ang, H.; Chen, X.; Wu, J. Strain-Release-Driven Electrochemical Skeletal Rearrangement of Non-Biased Alkyl Cyclopropanes/Butanes. *Angew. Chem. Int. Ed.* **2025**, *64* (1), e202413723. https://doi.org/10.1002/anie.202413723

14.4



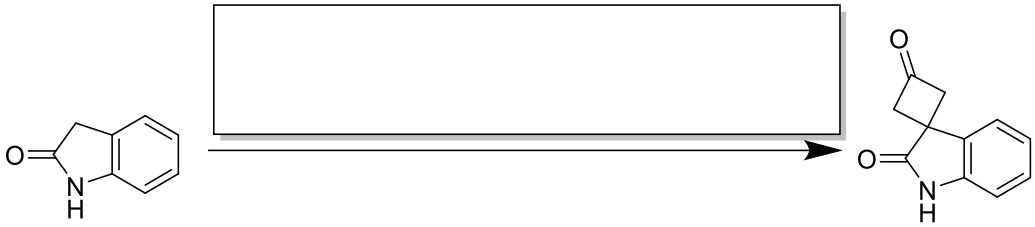
Chomicki, D.; Kharchenko, O.; Kaczmarek-Kędziera, A.; Czaplicki, R.; Krupka, O.; Kowalska, D.; Jahani, S. A.; Smokal, V.; Derkowska-Zielinska, B. Thermal Isomerization Rates of New Azoquinoline-Functionalized Copolymers as a Function of Substitution Patterns. *ChemPhysChem* **2025**, *26* (12), e202401155. https://doi.org/10.1002/cphc.202401155

14.5



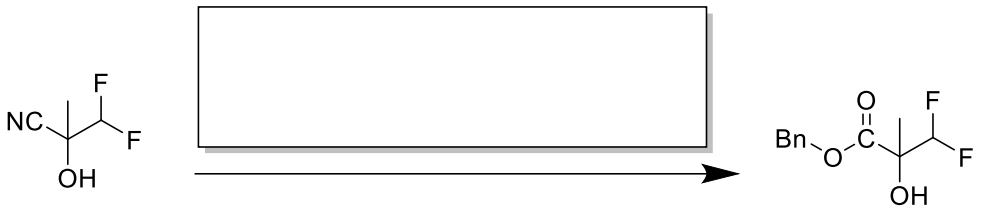
Bunnage, M. E.; Chippindale, A. M.; Davies, S. G.; Parkin, R. M.; Smith, A. D.; Withey, J. M. Asymmetric Synthesis of (1R,2S,3R)-3-Methylcispentacin and (1S,2S,3R)-3-Methyltranspentacin by Kinetic Resolution of *tert*-Butyl (±)-3-Methylcyclopentene-1-carboxylate. *Org. Biomol. Chem.* **2003**, *1* (21), 3698-3707. https://doi.org/10.1039/B306935B

14.6



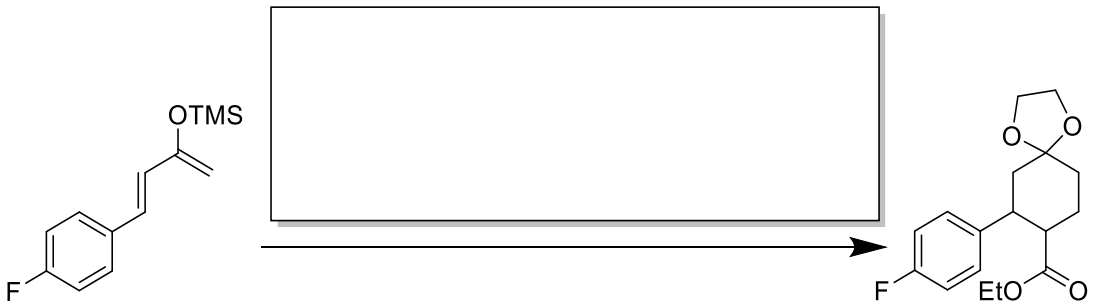
Cao, T. D. C.; Neufeld, K.; Zarate, C.; Nichols, C. J.; Lellek, V.; Deidda, R.; Conza, M.; Schleiss, P.; Rinderhagen, H.; Pye, P.; Muuronen, M.; Chen, W.; Tona, V.; Jouffroy, L.; Viereck, P.; Matcha, K. An Expedient Synthetic Route to the Long-Acting RSV Inhibitor JNJ-6231 via Stereoselective Enzymatic Amination and Regioselective Alkylation. *Org. Process Res. Dev.* **2026**, *30* (1), 121-134. https://doi.org/10.1021/acs.oprd.5c00352

14.7



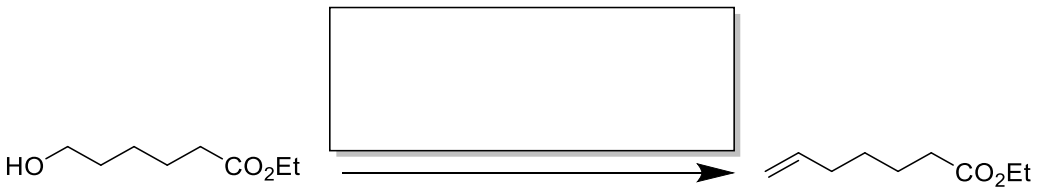
Cao, T. D. C.; Neufeld, K.; Zarate, C.; Nichols, C. J.; Lellek, V.; Deidda, R.; Conza, M.; Schleiss, P.; Rinderhagen, H.; Pye, P.; Muuronen, M.; Chen, W.; Tona, V.; Jouffroy, L.; Viereck, P.; Matcha, K. An Expedient Synthetic Route to the Long-Acting RSV Inhibitor JNJ-6231 via Stereoselective Enzymatic Amination and Regioselective Alkylation. *Org. Process Res. Dev.* **2026**, *30* (1), 121-134. https://doi.org/10.1021/acs.oprd.5c00352

14.8



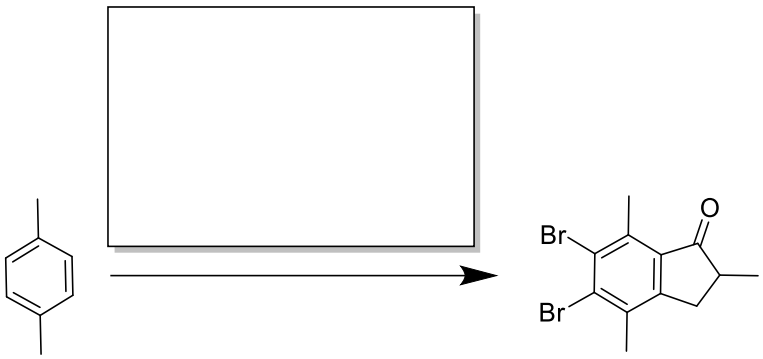
Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in *sp*^{3}-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

14.9



Vulovic, B.; Trmcic, M.; Matovic, R.; Saicic, R. N. Cyclization Reactions of Oxyallyl Cation. A Method for Cyclopentane Ring Formation. *Org. Lett.* **2019**, *21* (23), 9618–9621. https://doi.org/10.1021/acs.orglett.9b03791

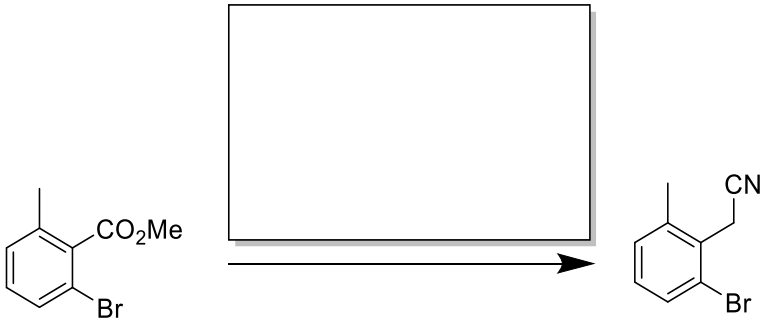
14.10



The authors did not use a Lewis acid in step 2 for the reaction to work.

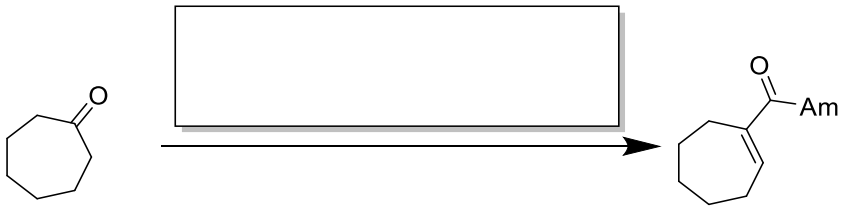
Kulyabin, P. S.; Sharikov, M. I.; Izmer, V. V.; Kononovich, D. S.; Goryunov, G. P.; Alexeev, N. V.; Uborsky, D. V.; Vittoria, A.; Antinucci, G.; Ehm, C.; Budzelaar, P. H. M.; Cipullo, R.; Busico, V.; Voskoboynikov, A. Z. Triptycene as a Scaffold in Metallocene Catalyzed Olefin Polymerization. *Dalton Trans.* **2024**, *53* (22), 9516-9525. https://doi.org/10.1039/D4DT01170H

14.11



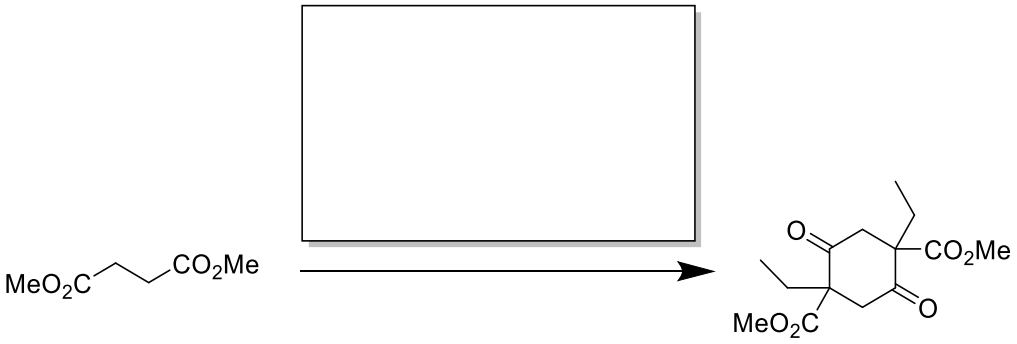
Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in *sp*^{3}-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

14.12



Scarpi, D.; Visi, S.; Muzzu, A.; Occhiato, E. G. One-Pot Gold(I)-Catalyzed Rautenstrauch Rearrangement/Nitrosocarbonyl Hetero-Diels–Alder Reaction Sequence for the Synthesis of α-Hydroxylated Cyclopentenones. *Eur. J. Org. Chem.* **2026**. *29* (27), e70611. https://doi.org/10.1002/ejoc.70611

14.13



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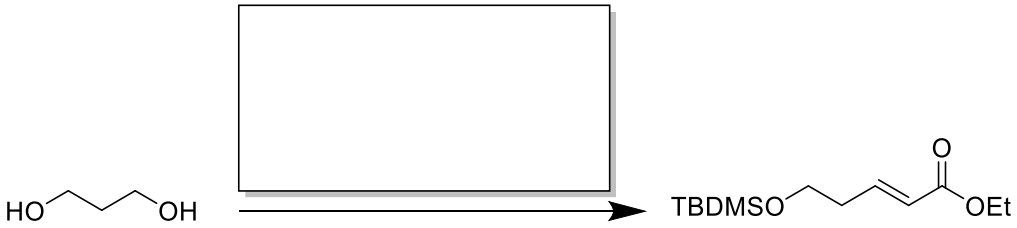

Step 2 and 3 are Swern oxidation conditions.

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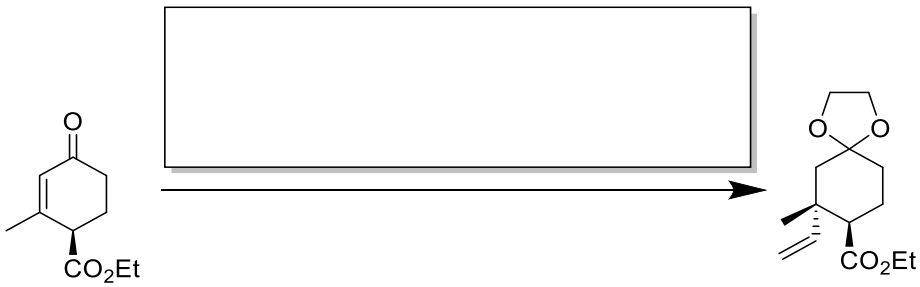

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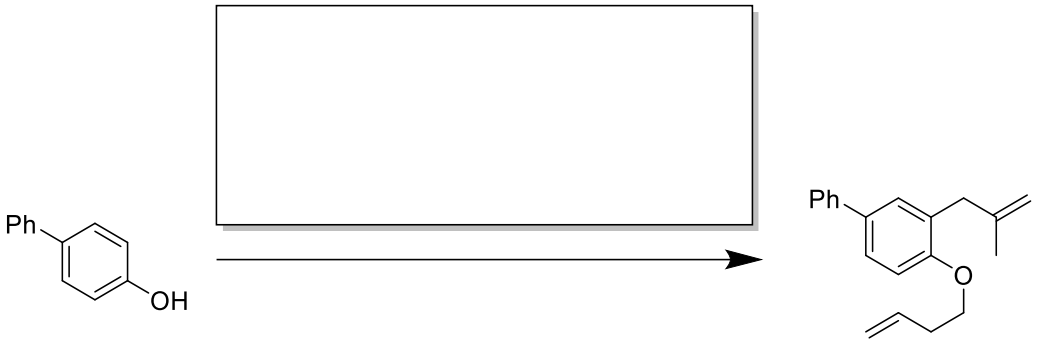

Nagafuchi, M.; Mizumachi, T.; Sato, Y.; Takatsuki, M.; Matsuzaki, T.; Suzuki, T.; Nakayama, A.; Sako, M.; Arisawa, M. Long-Range Isomerisation/Cyclopropane Isomerisation/Cycloisomerisation/Aromatisation Reactions Using Multifunctional Rhodium Catalysts. *Org. Biomol. Chem.* **2026**, *24* (22), 4605-4614. https://doi.org/10.1039/D6OB00534A

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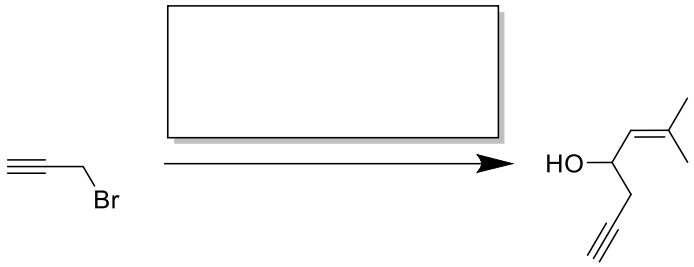

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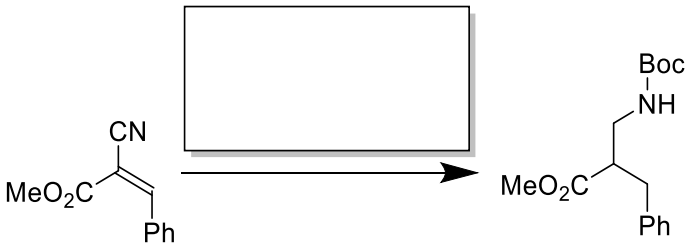

Narayanan, D.; Tran, K. T.; Pallesen, J. S.; Solbak, S. M. Ø.; Qin, Y.; Mukminova, E.; Luchini, M.; Vasilyeva, K. O.; González Chichón, D.; Goutsiou, G.; Poulsen, C.; Haapanen, N.; Popowicz, G. M.;

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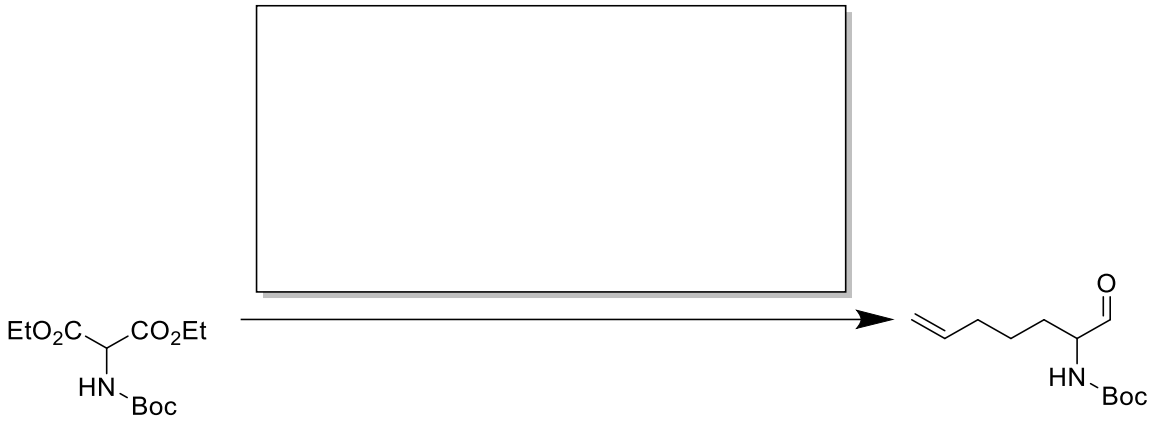

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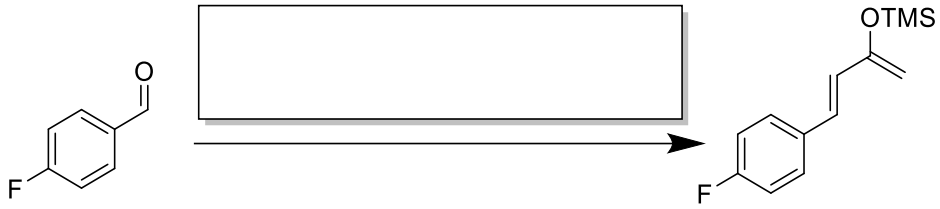
14.20



Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in *sp*^{3}-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

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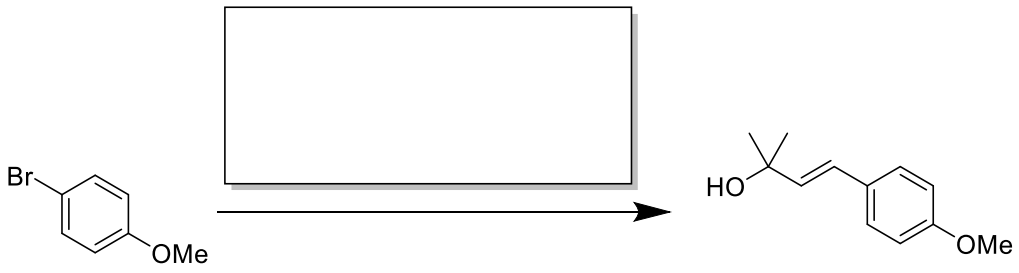

Tsai, S.; Huang, Y.; Chou, C. Carboxylate-Directed Palladium-Catalyzed Regioselective Mizoroki-Heck Alkenylation of *γ* , *δ* -Unsaturated Carboxylic Acids. *Adv. Synth. Catal.* **2023**, *365* (5), 699–703. https://doi.org/10.1002/adsc.202201317

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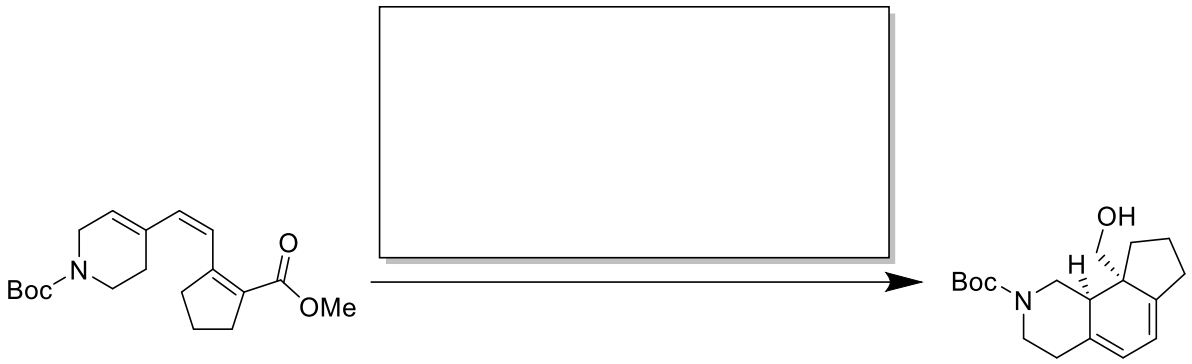

Note: Potassium sodium tartrate is a weak acid.

Krieger, J.-P.; Ricci, G.; Lesuisse, D.; Meyer, C.; Cossy, J. Efficient and Modular Synthesis of New Structurally Diverse Functionalized [*n*]Paracyclophanes by a Ring-Distortion Strategy. *Angew. Chem. Int. Ed.* **2014**, *53* (33), 8705-8708. https://doi.org/10.1002/anie.201401070

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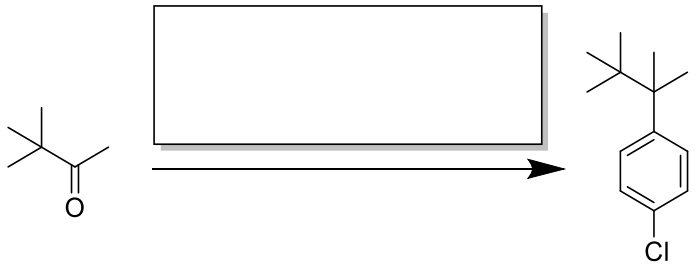

Yang, K.; He, S.; Huang, Y.; Xu, T.; Wang, Y.; Liu, K.; Zhang, L.; Ai, W.; Li, D.; Shen, T. Electrooxidative C-C Fragmentation of Aromatic Radical Cations for Cascade Benzylic Multifunctionalization. *Angew. Chem. Int. Ed.* **2026**, *65* (12), e22498. https://doi.org/10.1002/anie.202522498

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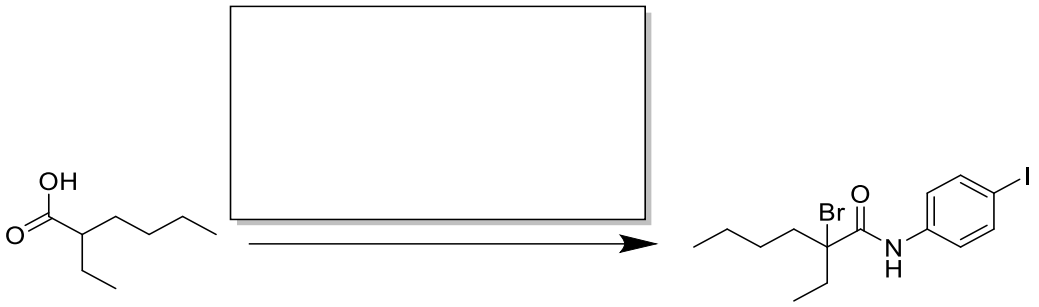

Tsuchiya, N.; Iwashita, I.; Yamamoto, T.; Akagawa, H.; Nishikata, T. Lewis Acid Catalyzed Stereospecific Hydroxylation of Chiral Tertiary Alkyl Halides. *Chem. Lett.* **2024**, *53* (2), upae005. https://doi.org/10.1093/chemle/upae005

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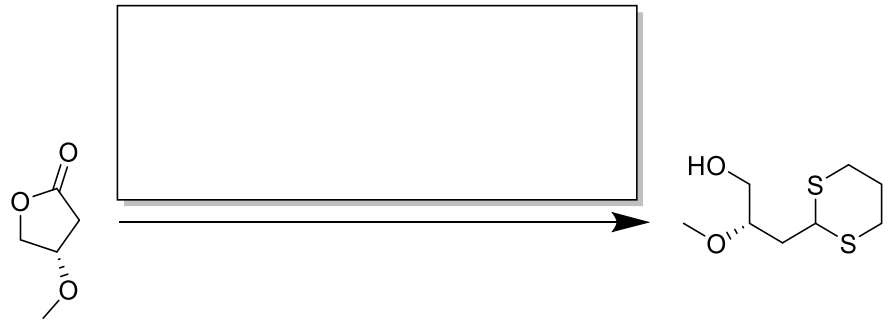

Ghidu, V. P.; Wang, J.; Wu, B.; Liu, Q.; Jacobs, A.; Marnett, L. J.; Sulikowski, G. A. Synthesis and Evaluation of the Cytotoxicity of Apoptolidinones A and D. *J. Org. Chem*. **2008**, *73* (13), 4949–4955. https://doi.org/10.1021/jo800545r

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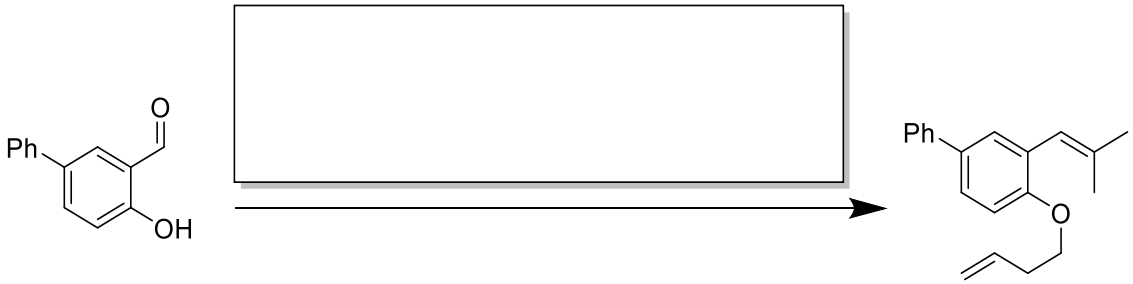

Nagafuchi, M.; Mizumachi, T.; Sato, Y.; Takatsuki, M.; Matsuzaki, T.; Suzuki, T.; Nakayama, A.; Sako, M.; Arisawa, M. Long-Range Isomerisation/Cyclopropane Isomerisation/Cycloisomerisation/Aromatisation Reactions Using Multifunctional Rhodium Catalysts. *Org. Biomol. Chem.* **2026**, *24* (22), 4605-4614. https://doi.org/10.1039/D6OB00534A

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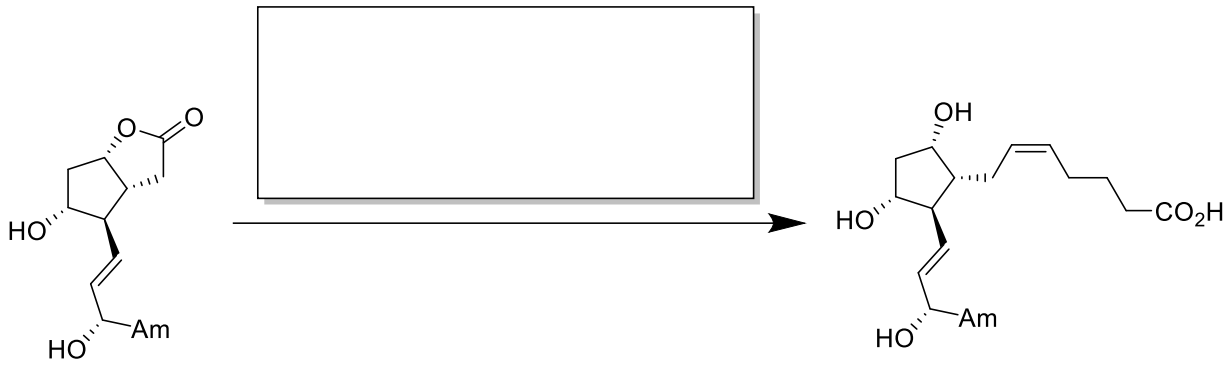

Yin, Y.; Wang, J.; Li, J. A Concise and Scalable Chemoenzymatic Synthesis of Prostaglandins. *Nat. Commun.* **2024**, *15* (1), 2523. https://doi.org/10.1038/s41467-024-46960-y

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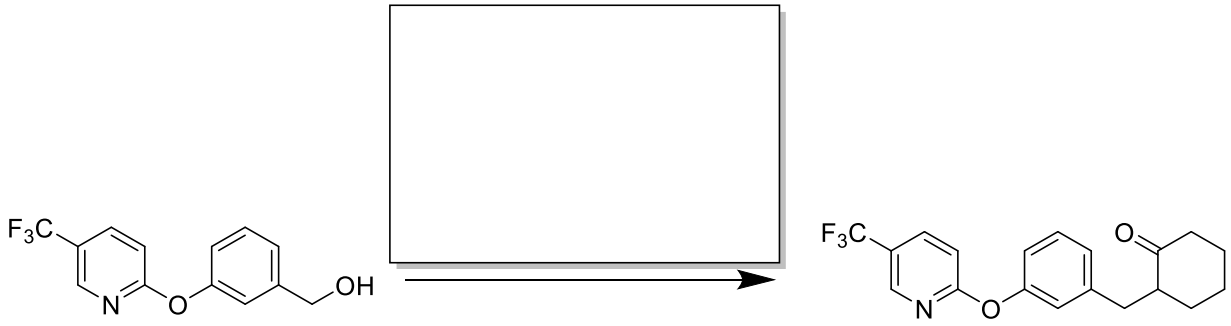

Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in *sp*^{3}-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

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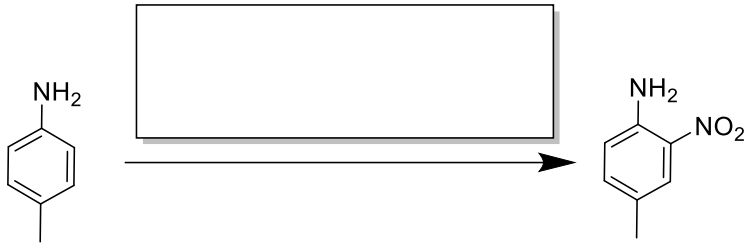

Glišić, B. Đ.; Hoffmann, M.; Warżajtis, B.; Genčić, M. S.; Blagojević, P. D.; Radulović, N. S.; Rychlewska, U.; Djuran, M. I. Selectivity of the Complexation Reactions of Four Regioisomeric Methylcamphorquinoxaline Ligands with Gold(III): X-Ray, NMR and DFT Investigations. *Polyhedron* **2016**, *105*, 137–149. https://doi.org/10.1016/j.poly.2015.12.009

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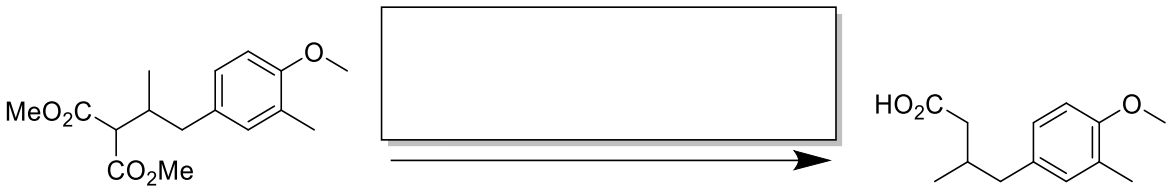

Note: Diglyme is an aprotic solvent with a high boiling point.

Roosen, P. C.; Karns, A. S.; Ellis, B. D.; Vanderwal, C. D. Evolution of a Short and Stereocontrolled Synthesis of (+)-7,20-Diisocyanoadociane. *J. Org. Chem.* **2022**, *87* (2), 1398–1420. https://doi.org/10.1021/acs.joc.1c02700

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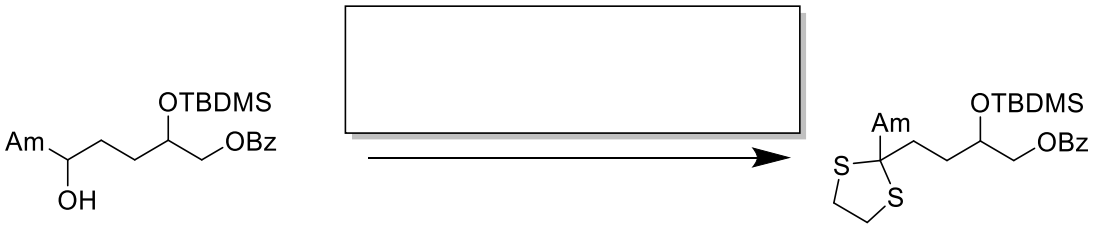

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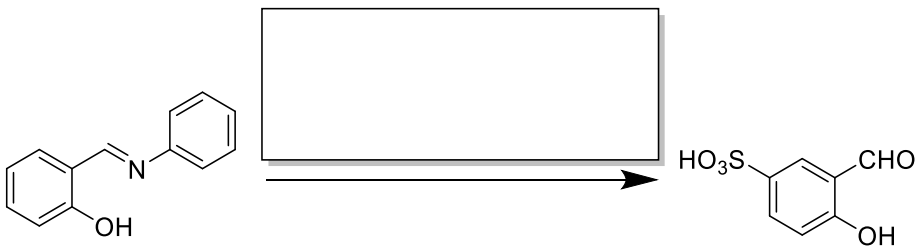

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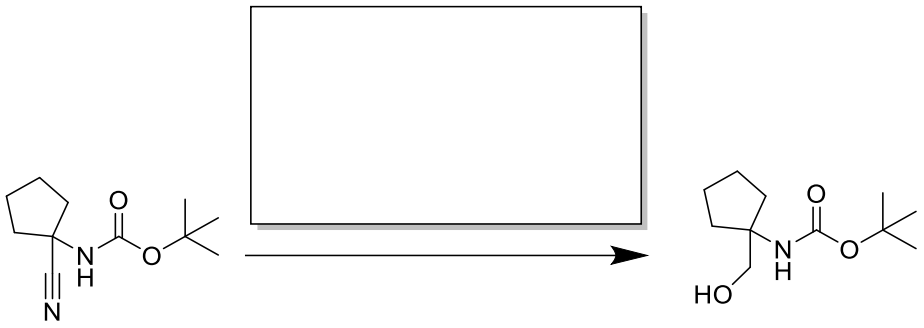

Zhang, Y.-H.; Jiao, F.-N.; Cao, F.-Y.; Zhao, M.-Z.; Sun, B.-Y.; Zhou, M.-J.; Xiao, H.; Dai, J.-J. Practical and Direct Synthesis of α-Aminonitriles Using N-Boc-O-tosyl Alkylhydroxylamines and TMSCN. *Chem. Commun*. **2026**, *62* (66), 16531–16535. https://doi.org/10.1039/D6CC03609K

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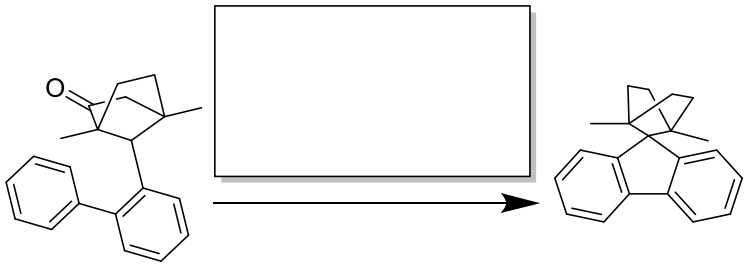


Note: AIBN reacts with NBS to generate a bromine radical.

Gu, Z.; Zeng, T.; Yuan, Z.; et al. Photocatalytic Stereoselective Editing of Alkynes to 3D Molecules via Hydrogen Atom Transfer-Mediated Dynamic Epimerization. *Nat. Commun*. **2026**, *17*, 2518. https://doi.org/10.1038/s41467-026-69219-0

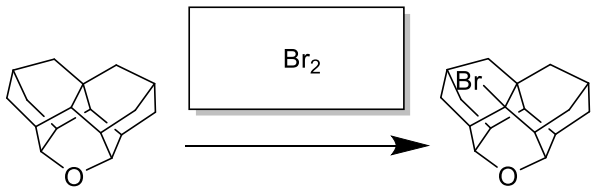
Section 15: Answers

Answers to all box-type and retrosynthesis questions.

Section 1 - Box-Type Questions

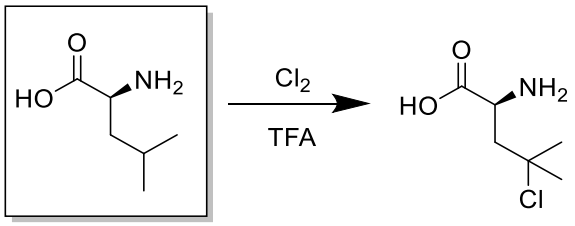
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

1.1.1



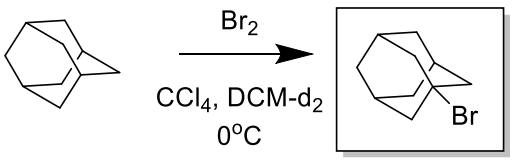
Fokin, A. A.; Zhuk, T. S.; Pashenko, A. E.; Dral, P. O.; Gunchenko, P. A.; Dahl, J. E. P.; Carlson, R. M. K.; Koso, T. V.; Serafin, M.; Schreiner, P. R. Oxygen-Doped Nanodiamonds: Synthesis and Functionalizations. *Org. Lett.* **2009**, *11* (14), 3068–3071. https://doi.org/10.1021/ol901089h

1.1.2



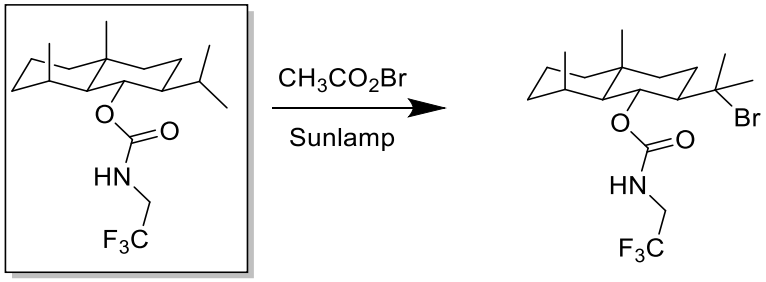
Watts, Z. I.; Easton, C. J. Peculiar Stability of Amino Acids and Peptides from a Radical Perspective. *J. Am. Chem. Soc.* **2009**, *131* (32), 11323–11325. https://doi.org/10.1021/ja9027583

1.1.3



Shernyukov, A. V.; Salnikov, G. E.; Krasnov, V. I.; Genaev, A. M. Cluster Halogenation of Adamantane and Its Derivatives with Bromine and Iodine Monochloride. *Org. Biomol. Chem.* **2022**, *20* (43), 8515–8527. https://doi.org/10.1039/D2OB01455F

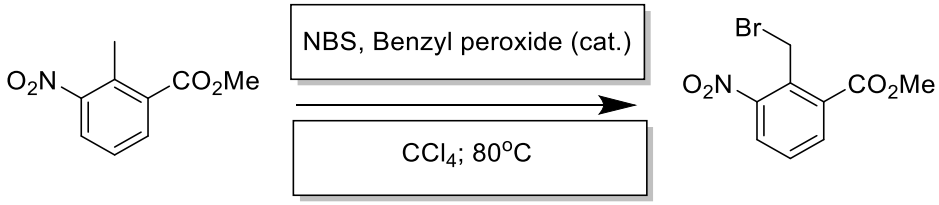
1.1.4



Note: CH_3CO_2Br (Acetyl hypobromite) undergoes a homolytic cleavage to give acyloxy and bromine radicals.

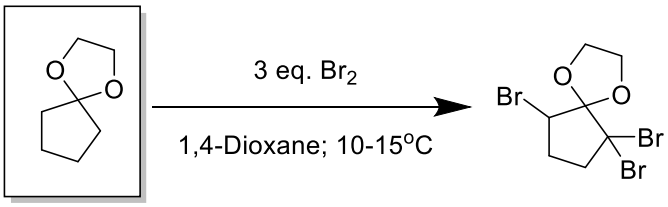
Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* **2009**, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

1.1.5



Sharma, K.; Strizhak, A. V.; Fowler, E.; Wang, X.; Xu, W.; Hatt Jensen, C.; Wu, Y.; Sore, H. F.; Lau, Y. H.; Hyvönen, M.; Itzhaki, L. S.; Spring, D. R. Water-Soluble, Stable and Azide-Reactive Strained Dialkynes for Biocompatible Double Strain-Promoted Click Chemistry. *Org. Biomol. Chem.* **2019**, *17* (34), 8014-8018. https://doi.org/10.1039/c9ob01745c

1.1.6



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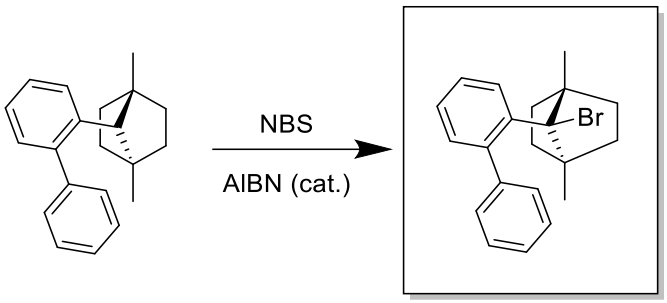
1.1.7



Note: AIBN reacts with NBS to generate a bromine radical.

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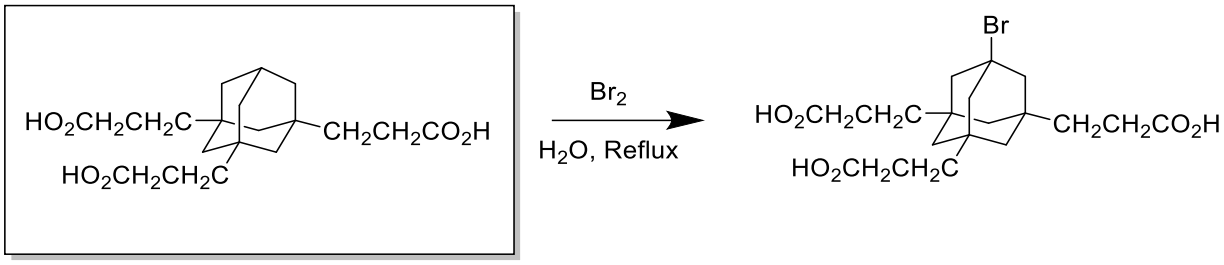
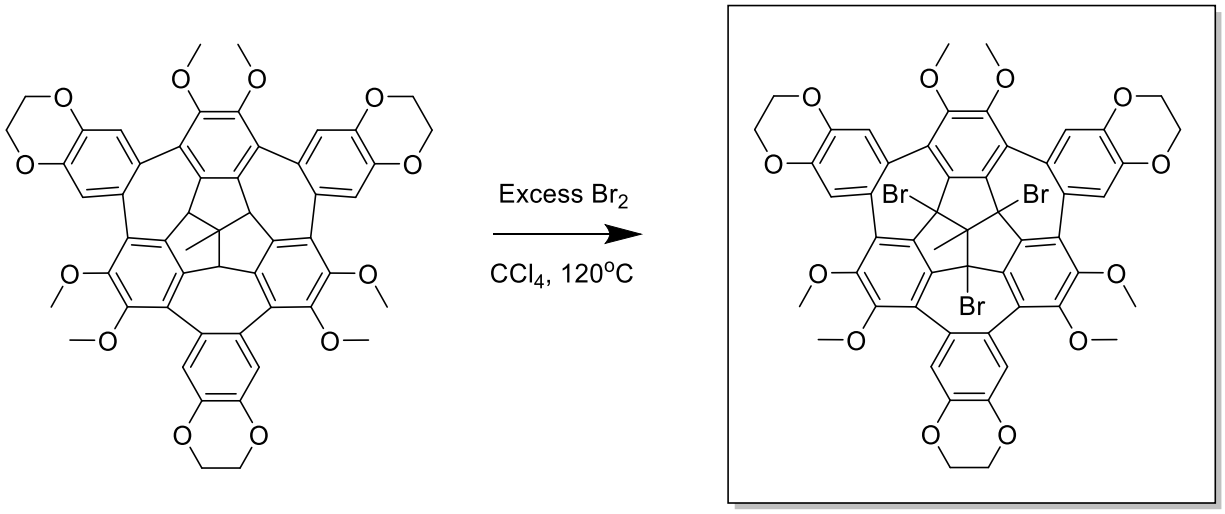
1.1.8



Note: The authors added CH_3CN to the reaction mixture to immediately convert the bromo product to an amide.

Maison, W.; Frangioni, J. V.; Pannier, N. Synthesis of Rigid Multivalent Scaffolds Based on Adamantane. *Org. Lett.* **2004**, *6* (24), 4567–4569. https://doi.org/10.1021/ol048055j

1.1.9



Hung, T.; Kuck, D.; Chow, H. Donor-Acceptor Tribenzotriquinacene-Based Molecular Wizard Hats Bearing Three *ortho*-Benzoquinone Units. *Chem. Eur. J. 2023*, **29** (18), e202203749. https://doi.org/10.1002/chem.202203749

Section 2 – Box-Type Questions

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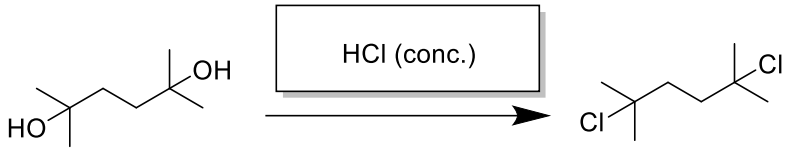
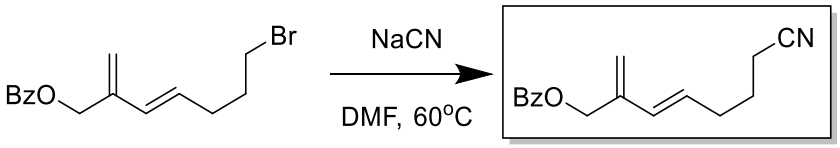
2.1.1



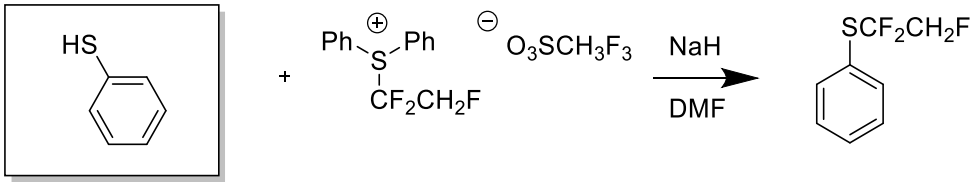
Wagner, C. E.; Marshall, P. A. Synthesis of 2,5-Dichloro-2,5-dimethylhexane by an SN1 Reaction. *J. Chem. Educ.* 2010, *87* (1), 81-83. https://doi.org/10.1021/ed8000057

2.1.2



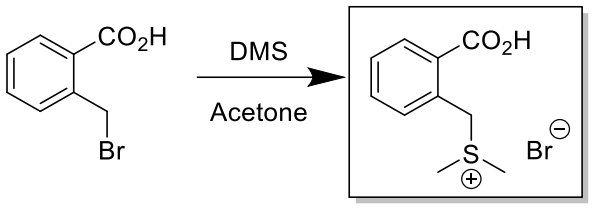
Ratsch, F.; Schmalz, H.-G. An Atom-Economic and Stereospecific Access to Trisubstituted Olefins through Enyne Cross Metathesis Followed by 1,4-Hydrogenation. *Synlett* 2018, *29* (06), 785–792. https://doi.org/10.1055/s-0036-1591528

2.1.3



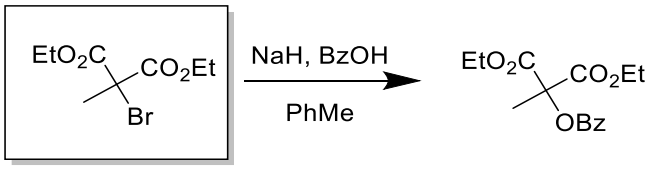
Majumder, S.; Alam, M. N.; Dolbier, W. R. Initial Investigation of the Direct Incorporation of the 1,1,2-Trifluoroethyl Substituent into Organic Compounds. *Org. Lett.* 2025, *27* (20), 5213–5217. https://doi.org/10.1021/acs.orglett.5c01403

2.1.4



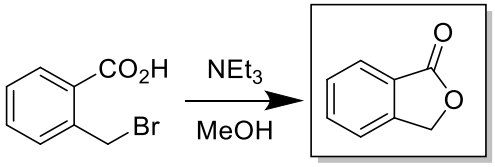
Pan, H.-L.; Kong, H.-H.; Ding, M.-W. One-Pot Synthesis of 3,4-Dihydroisoquinolin-1(2H)-Ones via a Sequential Ugi-4CR and Nucleophilic Substitution Reaction. *Tetrahedron* 2025, *178*, 134609. https://doi.org/10.1016/j.tet.2025.134609

2.1.5



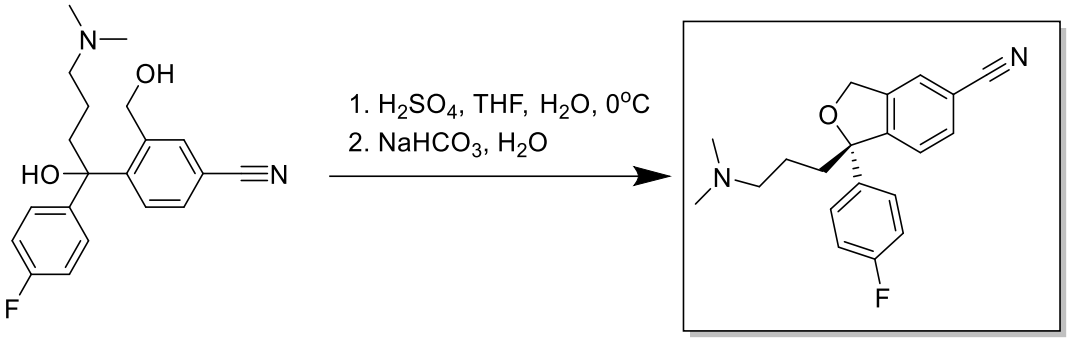
Monerris Mascaro, M.; Henderson, A. P.; Drozdowska, M.; Richardson, R.; Nagel-Savage, D.; Hall, M. J.; Longcake, A.; Mardiana, L.; Golding, B. T. Total Synthesis of 8-Hydroxy-Dihydroergotamine, the Major Human Metabolite of Dihydroergotamine. *Molecules* 2026, *31* (9), 1547. https://doi.org/10.3390/molecules31091547

2.1.6



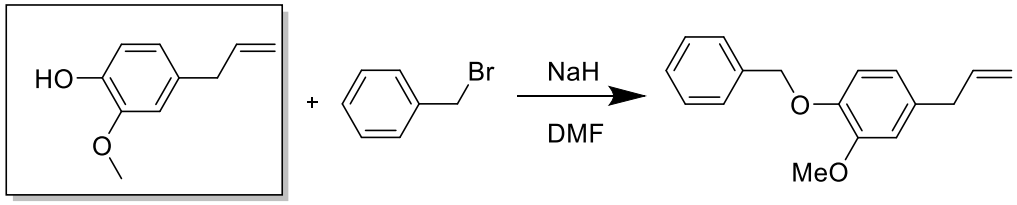
Pan, H.-L.; Kong, H.-H.; Ding, M.-W. One-Pot Synthesis of 3,4-Dihydroisoquinolin-1(2H)-Ones via a Sequential Ugi-4CR and Nucleophilic Substitution Reaction. *Tetrahedron* 2025, *178*, 134609. https://doi.org/10.1016/j.tet.2025.134609

2.1.7



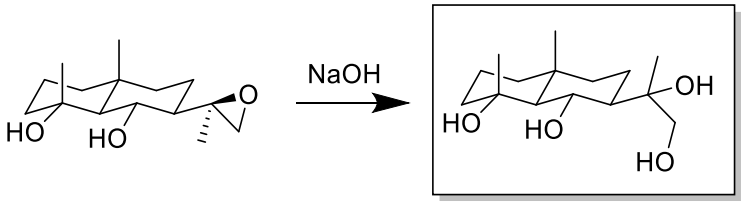
Liu, J.; Zheng, H.-X.; Yao, C.-Z.; Sun, B.-F.; Kang, Y.-B. Pharmaceutical-Oriented Selective Synthesis of Mononitriles and Dinitriles Directly from Methyl(hetero)arenes: Access to Chiral Nitriles and Citalopram. *J. Am. Chem. Soc*. 2016, *138* (10), 3294–3297. https://doi.org/10.1021/jacs.6b00180

2.1.8



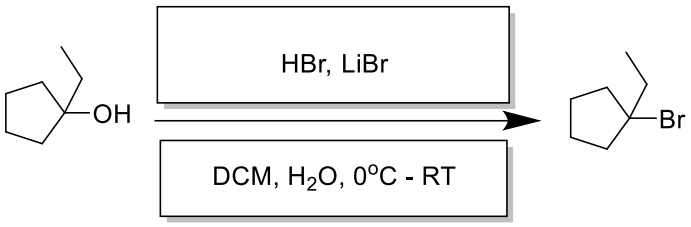
Shet, M. N.; Ramana, C. V. Total Synthesis of (−) and (+)-Zingibergingerols A. *J. Org. Chem.* 2024, *89* (22), 16923–16928. https://doi.org/10.1021/acs.joc.4c01649

2.1.9



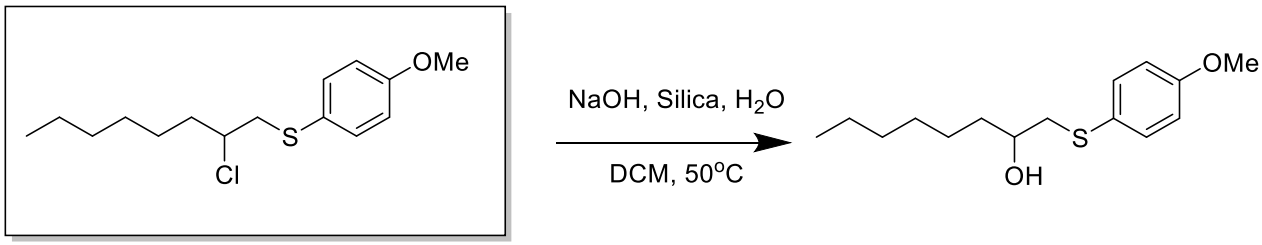
Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* 2009, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

2.1.10



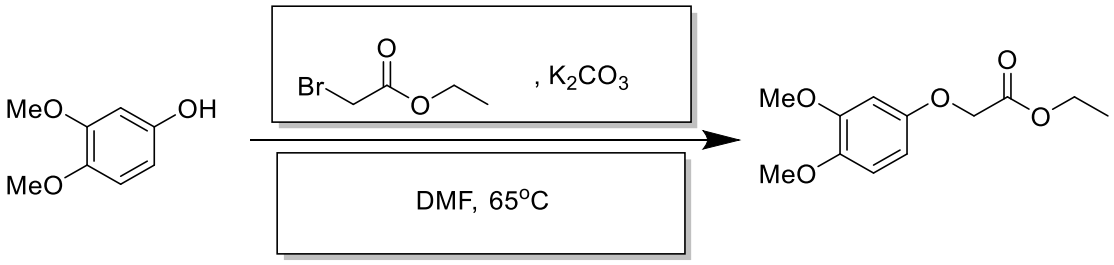
Chevet, L.; Durandetti, M.; Chausset-Boissarie, L. Electrochemical Generation of Alkyl Radicals from Boronic Esters for SOMOphilic Alkynylation. *Org. Lett*. 2026, *28* (5), 1709–1714. https://doi.org/10.1021/acs.orglett.5c05195

2.1.11



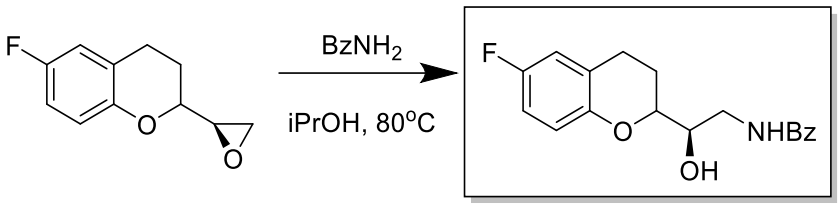
Xie, C.; Wang, Z.; Zhuang, W.; Liu, R.; Shi, C.; Liu, C.; Xu, Y.; Zhao, Y.; Li, X.; Shi, D. Photoinduced 1,2-Chlorothiolation of Unactivated Alkenes via Proton Transfer and Electron Transfer. *Org. Lett.* 2026, *28* (7), 2272–2277. https://doi.org/10.1021/acs.orglett.5c05294

2.1.12



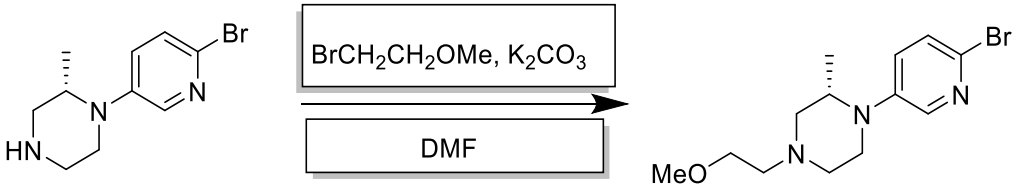
Ding, L.; An, Y.; Li, W.; Shangguan, H.; Tu, H.; Xu, X.; Shi, Y.; Liu, J.; Xie, Y. Design, Synthesis and Evaluation of Bis-3,4-Dimethoxybenzene-Based Fibrate Derivatives Guided by Structural Simplification and Bioisosterism Principle as Potential Hypolipidemic and Hepatoprotective Agents. *Bioorganic Chemistry* 2026, *173*, 109626. https://doi.org/10.1016/j.bioorg.2026.109626

2.1.13



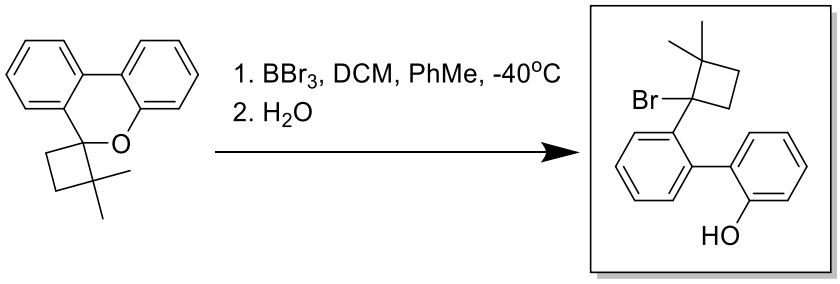
Ghosh, B.; Iglhaut, M.; Babushkina, D.; Pauls, M.; Bannwarth, C.; Bach, T. Photochemical Deracemization of Chromanes and Its Application to the Synthesis of Enantiopure Bioactive Compounds. *Angew. Chem. Int. Ed.* 2026, *65* (5), e21436. https://doi.org/10.1002/anie.202521436

2.1.14



Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* 2026, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

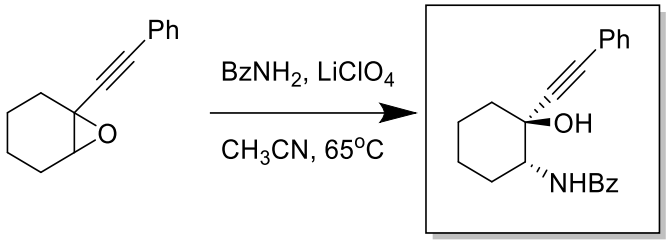
2.1.15



Hint: BBr_3 is a Lewis acid but also a source of bromide.

Geng, B.-H.; Hao, Z.-F.; Lu, Y.-H.; Liu, X.-L.; Li, A.-H.; Tian, P.; Li, Q.-H. Hexafluoroisopropanol-Enabled Access to Spirocyclobutanes via Cyclopropylcarbinyl Cation Rearrangement. *Org. Lett*. 2026, *28* (10), 3243–3248. https://doi.org/10.1021/acs.orglett.6c00248

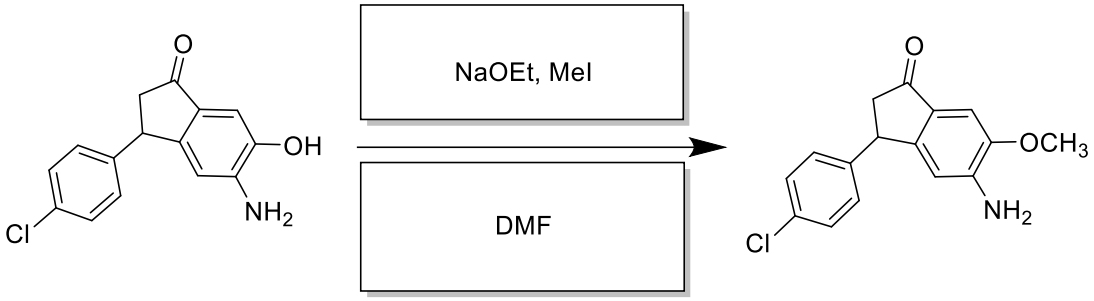
2.1.16



Note: For introductory organic chemistry courses, you can ignore the $LiClO_4$.

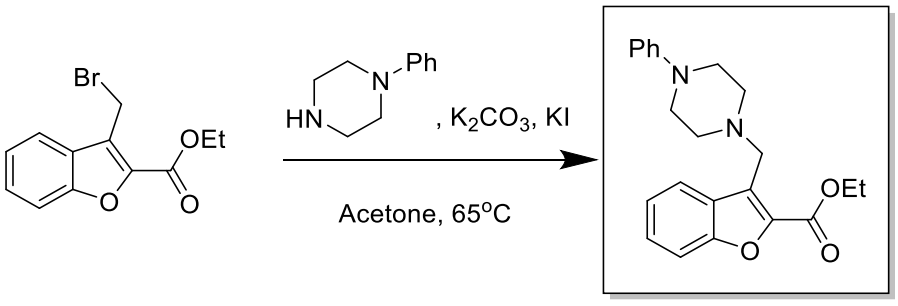
Belov, D. S.; Lukyanenko, E. R.; Kurkin, A. V.; Yurovskaya, M. A. Highly Stereoselective and Scalable Synthesis of *Trans* -Fused Octahydrocyclohepta[*b*]Pyrrol-4(1 *H*)-Ones via the Aza-Cope–Mannich Rearrangement in Racemic and Enantiopure Forms. *J. Org. Chem.* 2012, *77* (22), 10125–10134. https://doi.org/10.1021/jo301762a

2.1.17



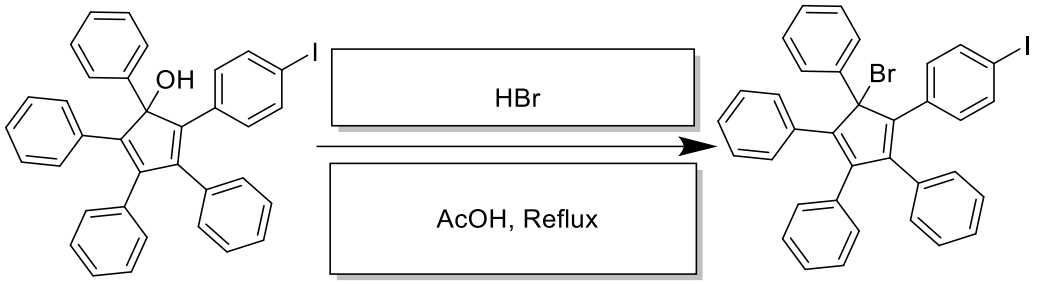
Park, C. H.; Siomboing, X.; Yous, S.; Gressier, B.; Luyckx, M.; Chavatte, P. Investigations of New Lead Structures for the Design of Novel Cyclooxygenase-2 Inhibitors. *Eur. J. Med. Chem.* 2002, *37* (6), 461–468. https://doi.org/10.1016/S0223-5234(02)01373-9.

2.1.18



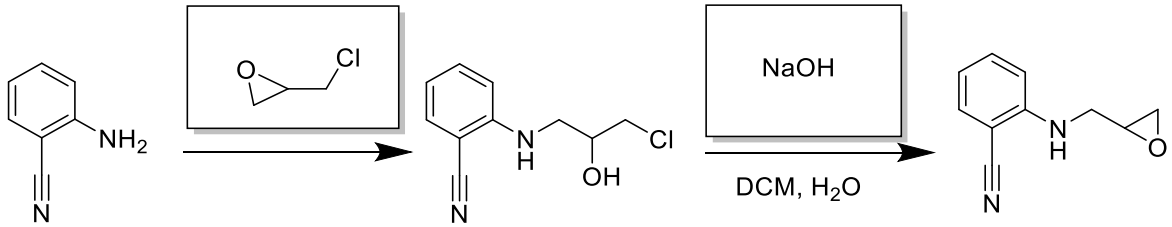
Eldehna, W. M.; Tawfik, H. O.; Nafie, M. S.; Al Kamaly, O.; El-Hamaky, A. A.; El Hassab, M. A.; Elsayed, Z. M.; Elnaggar, Y. S. R.; Al-Karmalawy, A. A.; di Giacomo, V.; Balaha, M. Novel Benzofuran-Conjugated Indolin-2-ones as Anticancer Agents: Design, Synthesis, Biological Assessments, and Molecular Modeling Insights. *Bioorg. Chem.* 2025, *160,* 108494. https://doi.org/10.1016/j.bioorg.2025.108494

2.1.19



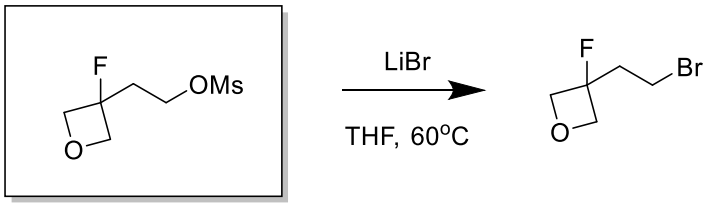
Nishino, T.; Ohno, Y.; Ishihara, M.; Nishikawa, Y.; Martin, C. J.; Yasuhara, K.; Rapenne, G. An Amphiphilic Pentaaryl Cyclopentadienyl Ruthenium(II) Molecular Rotor with a Luminescent Tag. *Synlett* 2025, *36* (9), 1237–1241. https://doi.org/10.1055/a-2503-7748

2.1.20



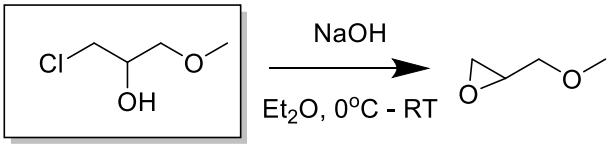
Lee, K.; Lee, X.; Zhou, C.-Y.; Chu, Y.-L.; Lin, C.-K. *Tert* -Butyl Carbonate as a Nucleophile in Epoxide Ring Opening: A Cascade Synthesis of 5-(Hydroxymethyl)Oxazolidin-2-One. *J. Org. Chem.* 2025, *90* (23), 7976–7981. https://doi.org/10.1021/acs.joc.5c00537

2.1.21



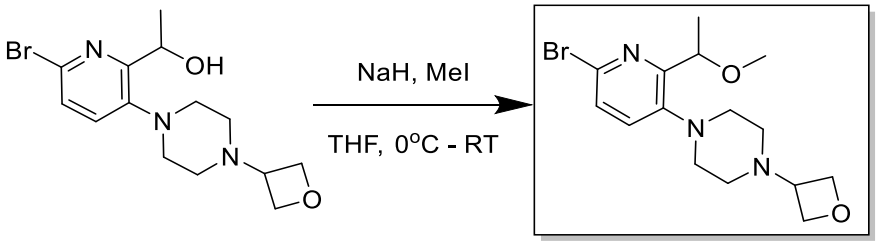
Litskan, E. V.; Lynnyk, S. V.; Shypov, R. H.; Vashchenko, B. V.; Hoida, A. Ye.; Klymenko-Ulianov, O. O.; Gorlova, A. O.; Granat, D. S.; Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V. Fine-Tuning of Physicochemical Properties of 3,3-Disubstituted Oxetanes Introducing Fluorine Atom(s) on the Building Blocks Level. *Chem. Eur. J.* 2025, *31* (51), e202500940. https://doi.org/10.1002/chem.202500940

2.1.22



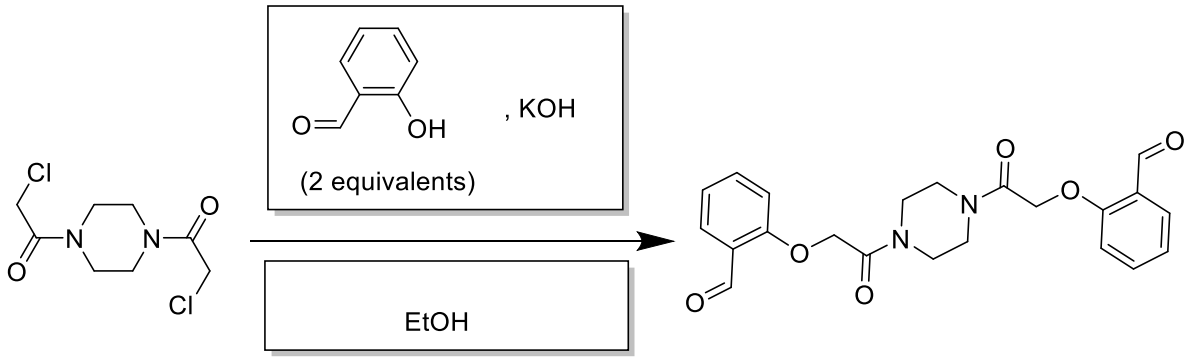
Mironov, V. F.; Nemtarev, A. V.; Tsepaeva, O. V.; Dimukhametov, M. N.; Litvinov, I. A.; Voloshina, A. D.; Pashirova, T. N.; Titov, E. A.; Lyubina, A. P.; Amerhanova, S. K.; Gubaidullin, A. T.; Islamov, D. R. Rational Design 2-Hydroxypropylphosphonium Salts as Cancer Cell Mitochondria-Targeted Vectors: Synthesis, Structure, and Biological Properties. *Molecules* 2021, *26* (21), 6350. https://doi.org/10.3390/molecules26216350

2.1.23



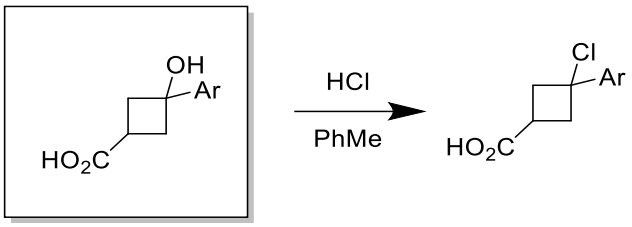
Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* 2026, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

2.1.24



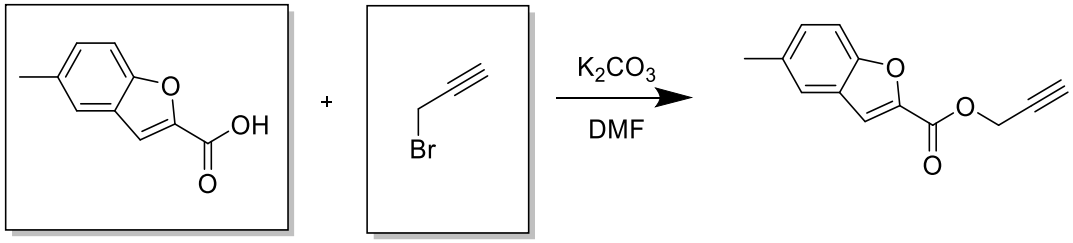
Alsulami, M. R.; Salem, M. E.; Abdelhamid, I. A.; Elwahy, A. H. M.; Barakat, K.; Abdelmoniem, A. M.; Raza, N.; Abdelwahab, R. E. Novel Bis(1,3,4a,9-Tetraza-4H-Fluoren-2-Amine) Derivatives: Synthesis, Antibacterial Activities, and Molecular Docking. *J. Mol. Struct.* 2026, *1349*, 143904. https://doi.org/10.1016/j.molstruc.2025.143904

2.1.25



Hazra, S.; Patel, M.; Mondal, S.; Ahmed, R.; Sasmal, P.; De, S.; Saha, J. Lewis Acid Catalyzed Dual Strain-Release Platform for Transforming Azabicyclo[1.1.0]butanes into Functionalized Azetidines with Donor-Acceptor (D-A) Cyclopropanes and Bicyclo[1.1.0]butanes. *Org. Lett.* 2026, *28* (14), 4554-4559. https://doi.org/10.1021/acs.orglett.6c00880

2.1.26

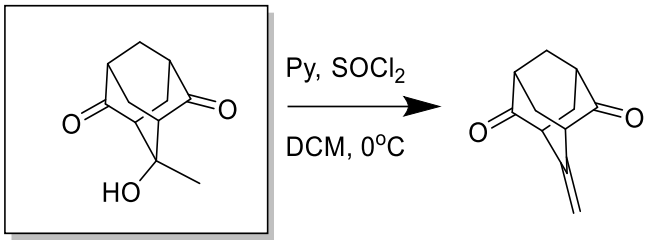


Sulakhe, S. M.; Khanzode, A. K.; Jamale, S. E.; Singh, M. B.; Singh, P.; Kumari, J.; Sriram, D.; Vedpathak, S. G.; Haval, K. P. New Benzofuran-Triazole-Tetrazole Conjugates: Synthesis, Antitubercular Evaluation, Molecular Docking, DFT, and MD Simulation. *J. Mol. Struct*. 2027, *1379*, 147348. https://doi.org/10.1016/j.molstruc.2026.147348

Section 3 – Box-Type Questions

For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

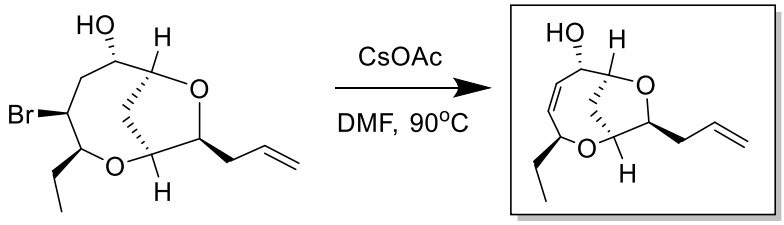
3.1.1



Hint: $SOCl_2$ converts an OH group into a Cl. Treat Py as a bulky base.

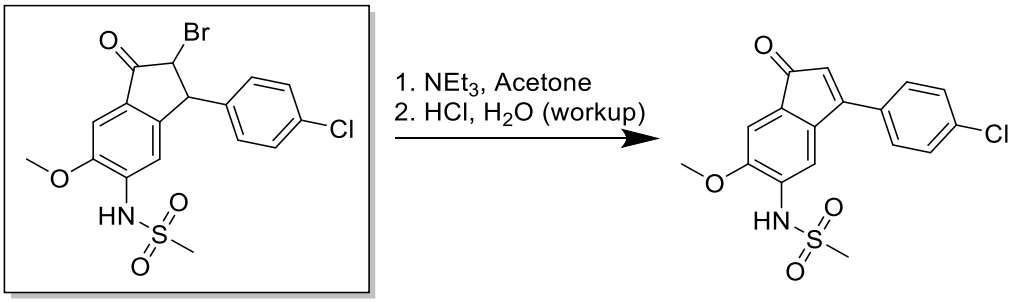
Ling, Y.; Zhang, P.; Sun, L.; Lai, W.; Luo, J. Efficient Synthesis of 2,2,4,4,6,6-Hexanitroadamantane under Mild Conditions. *Synthesis* 2014, *46* (16), 2225–2233. https://doi.org/10.1055/s-0033-1341251

3.1.2



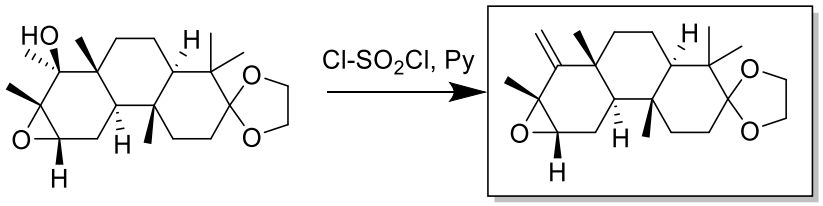
Chan, H. S. S.; Thompson, A. L.; Christensen, K. E.; Burton, J. W. Forwards and Backwards – Synthesis of *Laurencia* Natural Products Using a Biomimetic and Retrobiomimetic Strategy Incorporating Structural Reassignment of Laurefurenynes C–F. *Chem. Sci.* 2020, *11* (42), 11592–11600. https://doi.org/10.1039/D0SC04120C

3.1.3



Park, C. H.; Siomboing, X.; Yous, S.; Gressier, B.; Luyckx, M.; Chavatte, P. Investigations of New Lead Structures for the Design of Novel Cyclooxygenase-2 Inhibitors. *Eur. J. Med. Chem.* 2002, *37* (6), 461–468. https://doi.org/10.1016/S0223-5234(02)01373-9

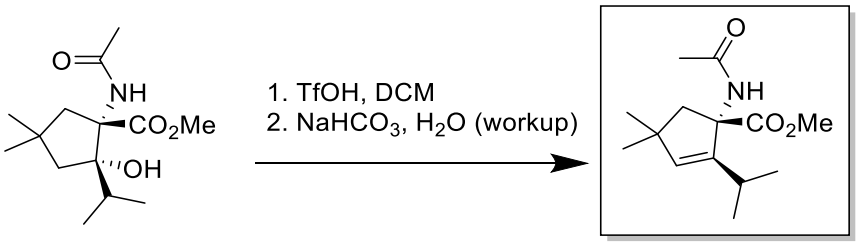
3.1.4



Note: SO_2Cl_2 is analogous to $SOCl_2$.

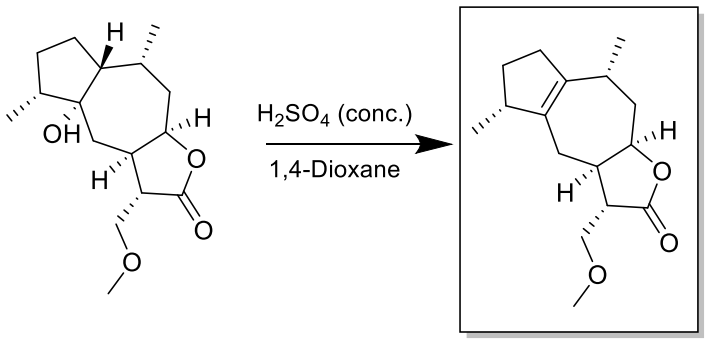
Takikawa, H.; Hirooka, M.; Sasaki, M. The First Synthesis of (±)-Brevione B, an Allelopathic Agent Isolated from Penicillium Sp. *Tetrahedron Lett.* 2003, *44* (28), 5235–5238. https://doi.org/10.1016/S0040-4039(03)01275-9

3.1.5



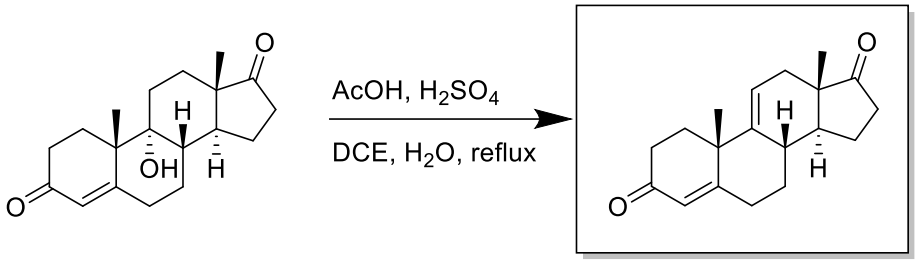
Yamamoto, R.; Qi, X.; Tsukiji, K.; Kwon, E.; Shi, L.; Yoshikai, N. Redox-Neutral Radical−Polar Crossover [3+2] Annulation of Cyclopropanols and Alkenes. *ACS Catalysis* 2026, *16* (9), 7972–7978. https://doi.org/10.1021/acscatal.6c01346

3.1.6



Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* 2024, *26* (22), 4648–4653. https://doi.org/10.1021/acs.orglett.4c01374

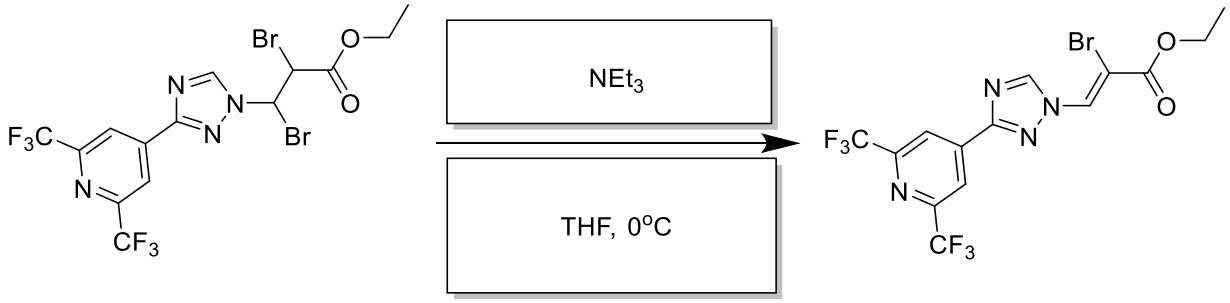
3.1.7



Hint: The product is not what you may expect to be the most stable product.

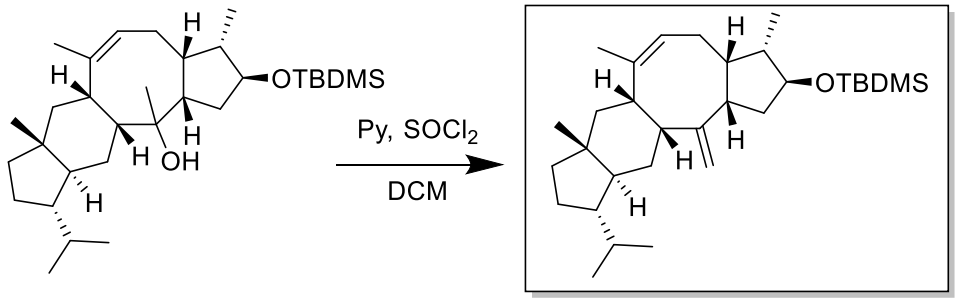
Wei, J.; Zhang, Y.; Liu, M.; Ning, Y.; Cao, Y.; Chen, F. Divergent Chemo- and Biocatalytic Route to 16 *β* -Methylcorticoids: Asymmetric Synthesis of Betamethasone Dipropionate, Clobetasol Propionate, and Beclomethasone Dipropionate. *Angew. Chem. Int. Ed.* 2024, *63* (4), e202313952. https://doi.org/10.1002/anie.202313952

3.1.8



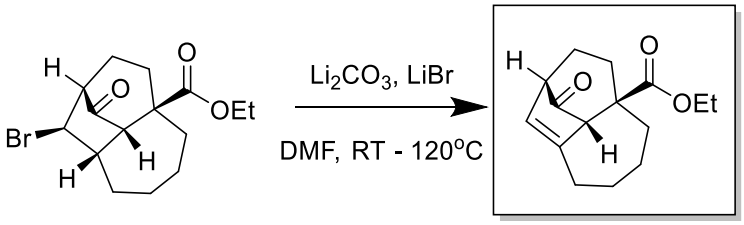
Miao, H.; Qin, Y.; Shao, D.; Chen, Q.; Pan, Y.; Lei, M.; Wu, R.; Ye, X.; Wang, X.; Zhu, Y. Discovery of SZJK-0421: A Novel Potent, Low Toxicity, Selective Second Generation of CRM1 Inhibitor for the Treatment of Both Hematological and Solid Tumors. *J. Med. Chem.* 2024, *67* (22), 20595–20618. https://doi.org/10.1021/acs.jmedchem.4c02169

3.1.9



Paquette, L. A. Studies Directed to the Synthesis of the Antifungal Antibiotic Aleurodiscal. Enantioselective Construction of an Advanced β-D-Xyloside Congener. *Synthesis* 1998, *1998* (Spec. Issue), 495-508. https://doi.org/10.1055/s-1998-5921

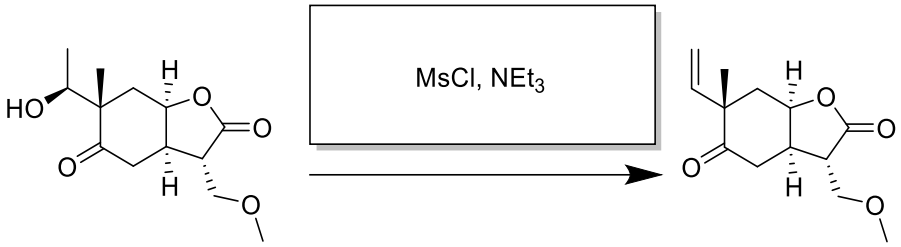
3.1.10



Hint: The bromide of LiBr does a substitution reaction first.

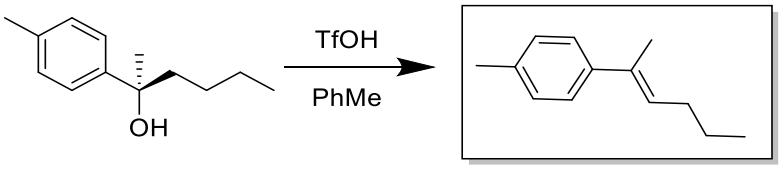
Cao, S.-Y.; Yue, H.-J.; Zhu, M.-Q.; Xu, L. Synthesis of Tricyclo[7.2.1.0^{9,10}]Dodecan-11-One Core Ring Systems of Norditerpenoid Alkaloids and Racemulosine. *Org. Chem. Front.* 2020, *7* (7), 933–937. https://oi.org/10.1039/D0QO00088D

3.1.11



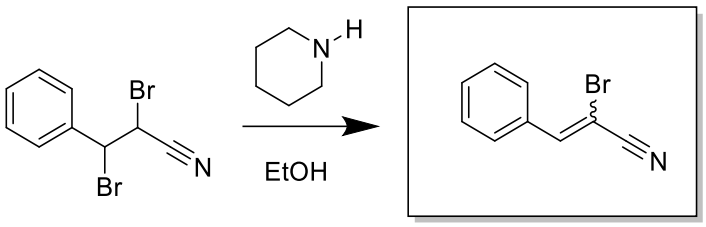
Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* 2024, *26* (22), 4648–4653. https://doi.org/10.1021/acs.orglett.4c01374

3.1.12



Kavanagh, S. E.; Monasterolo, C.; Gilheany, D. G. Enantiospecific Acid-Catalysed Hydroperoxidation of Scalemic Tertiary Benzylic Alcohols Facilitating a Concise Asymmetric Synthesis of Yingzhaosu C. *Eur. J. Org. Chem.* 2026, *29* (26), e70581. https://doi.org/10.1002/ejoc.70581

3.1.13

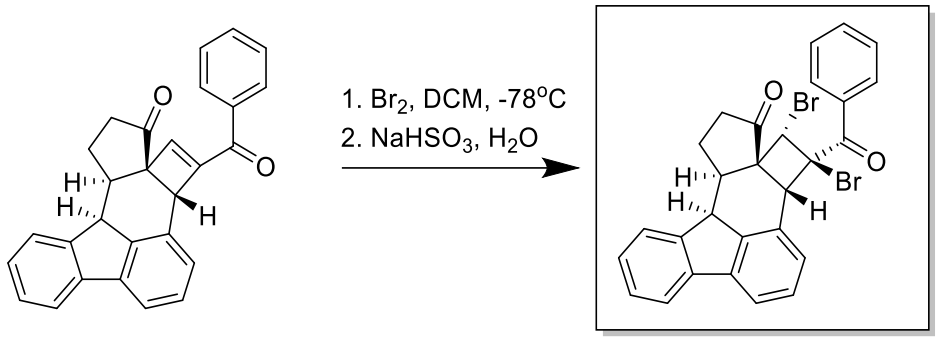


Thibonnet, J.; Vu, V. A.; Bérillon, L.; Knochel, P. Preparation of α-Functionalized Alkenylmagnesium Reagents via a Halide−Magnesium Exchange. *Tetrahedron* 2002, *58* (24), 4787–4799. https://doi.org/10.1016/S0040-4020(02)00439-8

Section 4a – Box-Type Questions

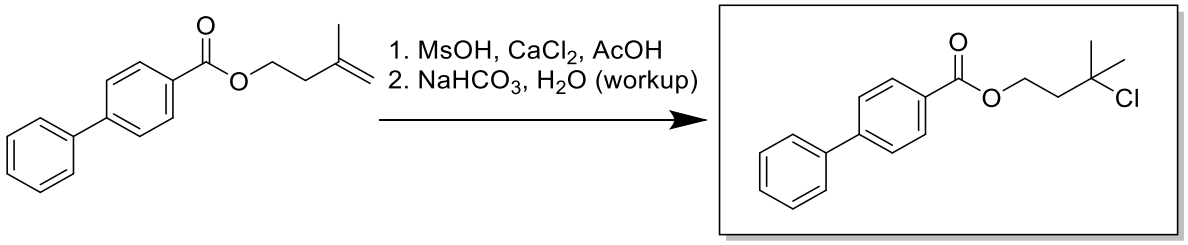
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

4a.1.1



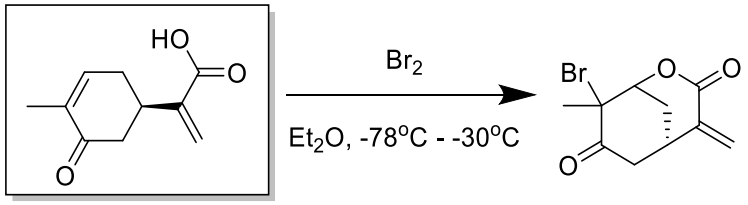
Corti, V.; Barløse, C. L.; Østergaard, N. L.; Kristensen, A.; Jessen, N. I.; Jørgensen, K. A. Organocatalytic Enantioselective Thermal [4 + 4] Cycloadditions. *J. Am. Chem. Soc.* 2023, *145* (2), 1448–1459. https://doi.org/10.1021/jacs.2c12750

4a.1.2



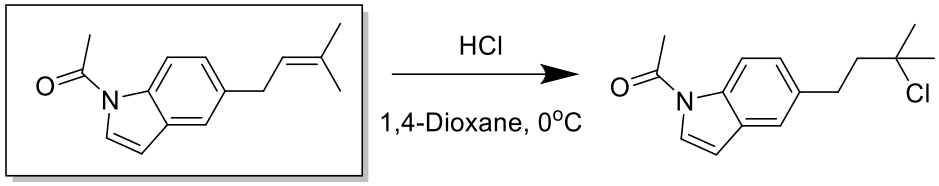
Bertrand, X.; Paquin, P.; Chabaud, L.; Paquin, J.-F. Hydrohalogenation of Unactivated Alkenes Using a Methanesulfonic Acid/Halide Salt Combination. *Synthesis* 2022, *54* (05), 1413–1421. https://doi.org/10.1055/s-0040-1719856

4a.1.3



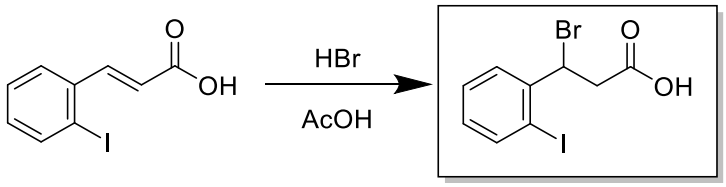
Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* 2024, *26* (22), 4648–4653. https://doi.org/10.1021/acs.orglett.4c01374

4a.1.4



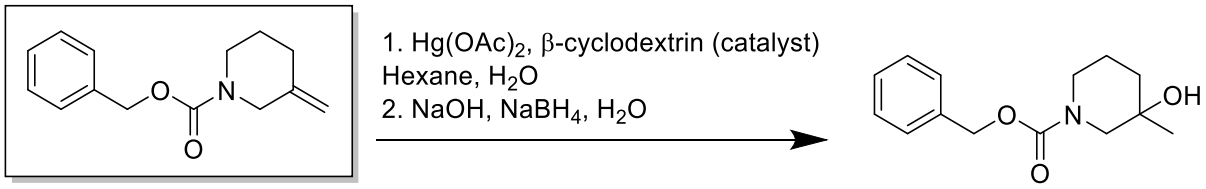
Devarajappa, R.; Hanessian, S. Total Synthesis of Asperdinones B, C, D, E and Tererezine D. *Beilstein J. Org. Chem.* 2025, *21*, 2730–2738. https://doi.org/10.3762/bjoc.21.210

4a.1.5



Liu, S.; Díaz-Fernández, M.; Zhang, M.; Huang, F.; Chen, Y.; Yang, Y.; Marín-Beloqui, J. M.; Lan, J.; You, J.; Casado, J.; Zhang, C. Azuperylene: The Nonalternant Isomer of Perylene. *Angew. Chem. Int. Ed.* 2025, *64* (29), e202505897. https://doi.org/10.1002/anie.202505897

4a.1.6



Note: You can ignore the use of β-cyclodextrin.

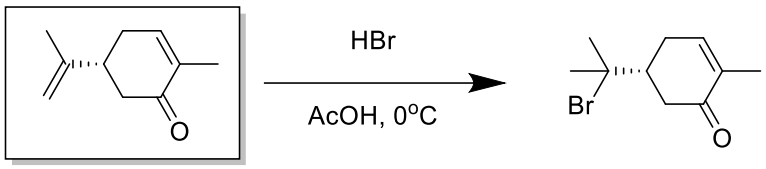
Abreu, A. R.; Costa, I.; Rosa, C.; Ferreira, L. M.; Lourenço, A.; Santos, P. P. New Enantioselective Method for Hydration of Alkenes Using Cyclodextrins as Phase Transfer Catalyst. *Tetrahedron* 2005, *61* (50), 11986–11990. https://doi.org/10.1016/j.tet.2005.09.064

4.1.7



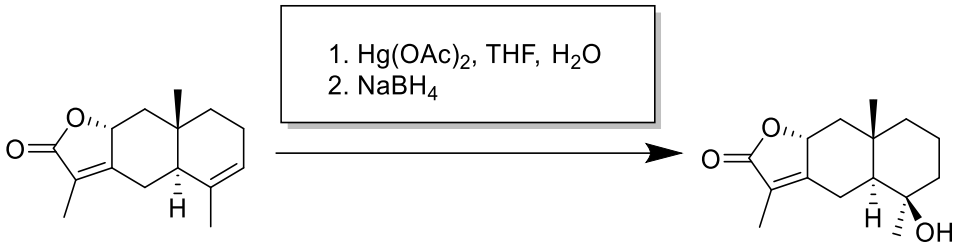
Zi, Q.; Min, L.; Du, H.; Yu, Q.; Li, Y.; Shu, W. Switchable Regiodivergent Reductive Alkyl–Alkyl Coupling by Nickel Catalysis: Sorting Different Alkyl–Nickel Intermediates. *Angew. Chem. Int. Ed.* 2025, *64* (30), e202507313. https://doi.org/10.1002/anie.202507313

4a.1.8



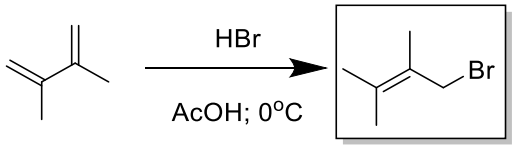
Mori, K. Absolute Configuration of Gomadalactones A, B and C, the Components of the Contact Sex Pheromone of *Anoplophora malasiaca*. *Tetrahedron Lett. 2007*, 48 (32), 5609–5611. https://doi.org/10.1016/j.tetlet.2007.06.054

4a.1.9



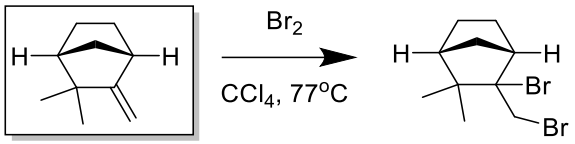
Sreelekshmi, S.; Kaliappan, K. P. A Unified Strategy to the Enantiomers of Atractylenolides and Related Eudesmane Sesquiterpenoids from (−)-Verbenone. *Org. Biomol. Chem.* 2026, *24* (32), 6564–6570. https://doi.org/10.1039/D6OB01041E

4a.1.10



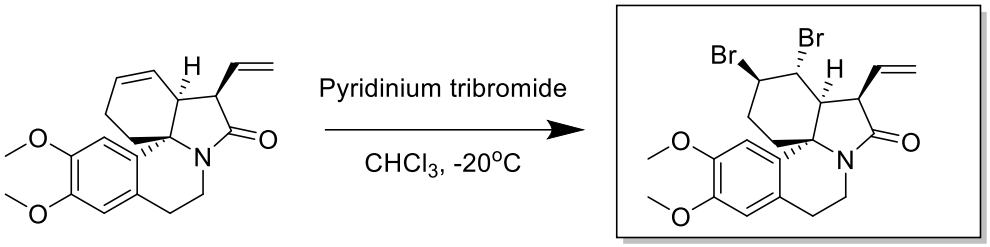
Lavernhe, R.; Wang, Q.; Zhu, J. [4+1] Heteroannulation to Form 1-Pyrrolines through Alder-Ene Reaction of in Situ Generated Ynimines: Development and Application in Total Synthesis of Borrecapine. *Angew. Chem. Int. Ed.* 2025, *64* (2), e202414612. https://doi.org/10.1002/anie.202414612

4a.1.11



Yılmaz, R. F.; Tutar, A.; Islam, M. Z.; Derin, Y.; Ökten, S.; Şahin, E.; Dastan, A. Photo-Induced Bromination of (+)-Camphene and Efficient Synthesis of Novel Camphene-Based Compounds. *SSRN* 2025. https://doi.org/10.2139/ssrn.5166613

4a.1.12

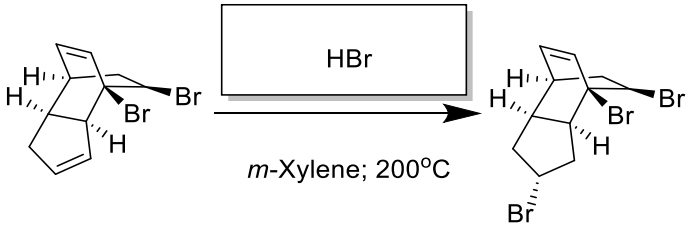


Note: Only one dibromide stereoisomer is shown, but both are assumed to form. Since the bromides are eliminated in the subsequent step, their stereochemistry was likely not considered important.

Note: Pyridinium tribromide is a source for molecular bromine.

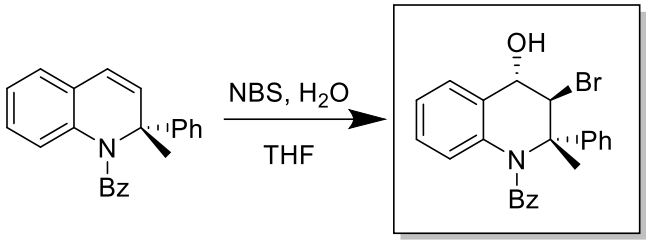
Zhang, F.; Simpkins, N. S.; Blake, A. J. New Approaches for the Synthesis of Erythrinan Alkaloids. *Org. Biomol. Chem.* 2009, *7* (9), 1963-1979. https://doi.org/10.1039/b900189a

4a.1.13



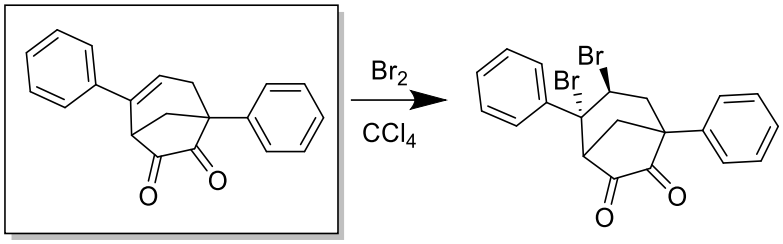
Su, K.-J.; Mieusset, J.-L.; Arion, V. B.; Brecker, L.; Brinker, U. H. Cope Rearrangement versus a Novel Tandem Retro-Diels−Alder−Diels−Alder Reaction with Role Reversal. *Org. Lett.* 2007, *9* (1), 113–115. https://doi.org/10.1021/ol0626793

4a.1.14



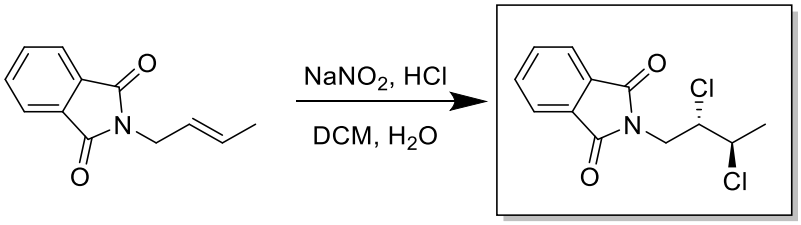
Huang, W.-J.; Chen, J.; Bai, Y.-Q.; Zhou, Y.-G.; Jiang, G.-F.; Wu, B. Asymmetric Synthesis of 2,2-Disubstituted Dihydroquinolines via Rhodium-Catalyzed Dearomative Arylation and Alkenylation of 2-Substituted Quinolinium Salts. *Org. Lett.* 2026, *28* (7), 2284–2288. https://doi.org/10.1021/acs.orglett.5c05303

4a.1.15



Liu, H.; Ji, D.-W.; Min, X.-T.; Mei, Y.-K.; Sun, S.-H.; Zhang, G.; Hu, Y.-C.; Chen, Q.-A. Disproportionation-Inspired Construction of Highly Functionalized Bicyclo[3.2.1]Octanes. *Org. Lett.* 2023, *25* (11), 1878–1882. https://doi.org/10.1021/acs.orglett.3c00397

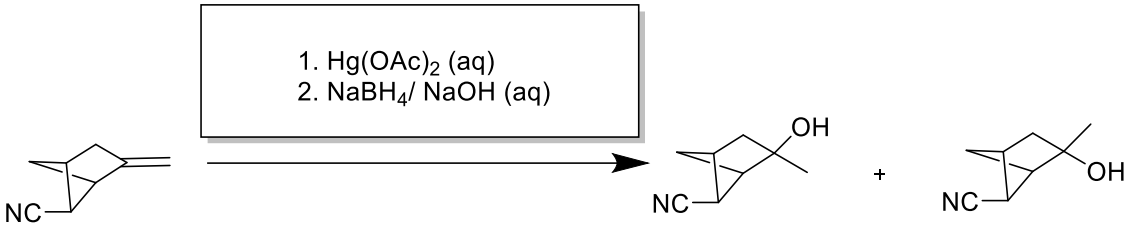
4a.1.16



Note: NO_2^- oxidizes Cl^- to yield molecular chlorine (Cl_2).

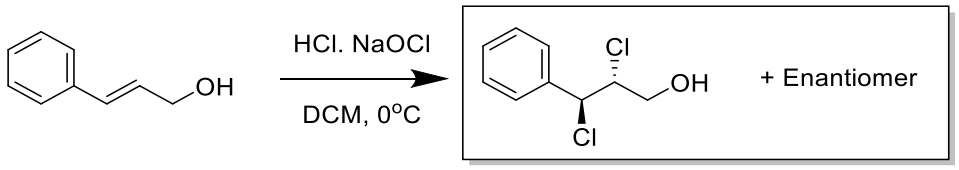
Nong, J.; Cao, Z.; He, Q.; Zhang, Y.; Chen, J.; Wang, Y. A Versatile, Tunable Method for $NaNO_2$ /HX (Cl or Br)-Mediated Radical Dihalogenation or Nitration of Olefins. *Green Chem.* 2025, *27* (46), 14883–14898. https://doi.org/10.1039/D5GC04596G

4a.1.17



Mehta, G.; Singh, S. R.; Balanarayan, P.; Gadre, S. R. Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]Hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects. *Org. Lett.* 2002, *4* (14), 2297–2300. https://doi.org/10.1021/ol026005d

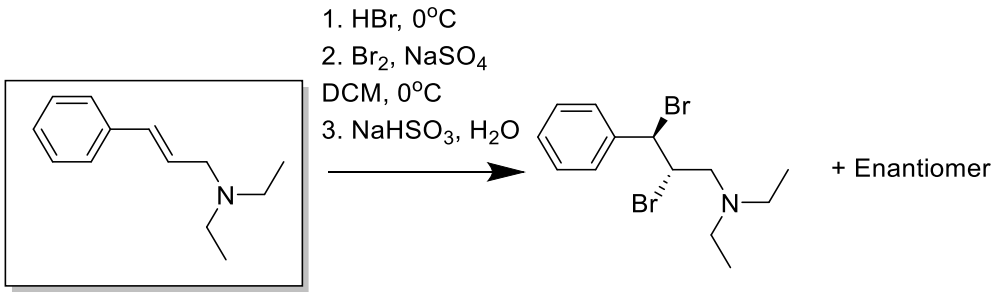
4a.1.18



Note: OCl^- oxidizes Cl^- to yield molecular chlorine.

Aguilar, G. C.; Lis, P. A.; Wise, D. E.; Martinez, J. S.; Parasram, M. Safe and Practical Ex-Situ Chlorination of Electronically Diverse π-Systems. *Tetrahedron Lett.* 2023, *124*, 154591. https://doi.org/10.1016/j.tetlet.2023.154591

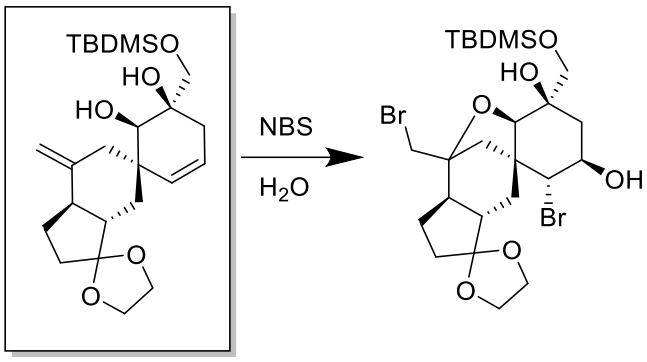
4a.1.19



Note: HBr hinders a certain atom's nucleophilicity.

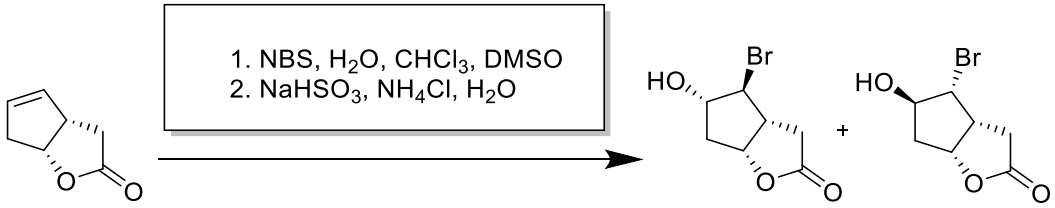
Ahrens, S.; Kusy, R.; Spannenberg, A.; Vuong, T. H.; Rabeah, J.; Russbueldt, B. M. E.; Panten, J.; Jiao, H.; Junge, K.; Beller, M. Cobalt(0)-Catalyzed Isomerization of Allylamines Promoted by Monodentate Benzofuran Phosphines. *J. Am. Chem. Soc.* 2025, *147* (35), 31859–31870. https://doi.org/10.1021/jacs.5c09017

4a.1.20



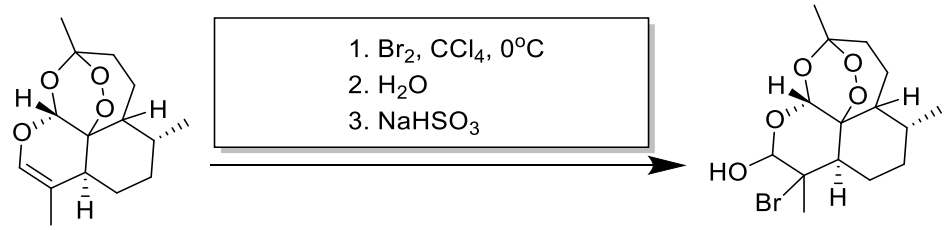
Zhang, Y.; Milkovits, A.; Agarawal, V.; Taylor, C. A.; Snyder, S. A. Total Synthesis of the Meroterpenoid Manginoid A as Fueled by a Challenging Pinacol Coupling and Bicycle-forming Etherification. *Angew. Chem. Int. Ed.* 2021, *60* (20), 11127–11132. https://doi.org/10.1002/anie.202016178

4a.1.21



Yin, Y.; Wang, J.; Li, J. A Concise and Scalable Chemoenzymatic Synthesis of Prostaglandins. *Nat. Commun.* 2024, *15* (1), 2523. https://doi.org/10.1038/s41467-024-46960-y

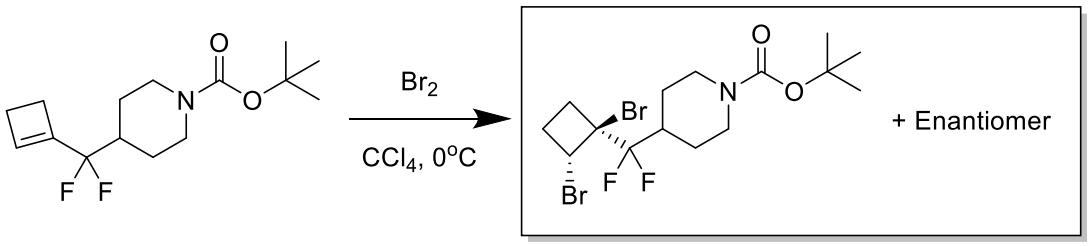
4a.1.22



Note: $NaHSO_3$ quenches excess bromine.

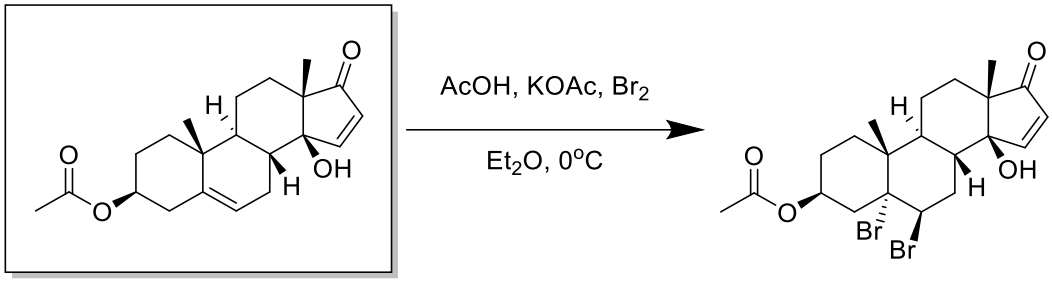
Qing, L.; Yu, Q.; Wang, C.; Lu, X.; Yang, Y.; Chen, X.; Li, X.; Min, J.; Pan, W.; He, H.; Zhong, H.; Zhang, S. Discovery of D-Ring-Contracted Artemisinin as a Potent Hydrophobic Tag for Targeted Protein Degradation. *J. Med. Chem.* 2025, *68* (2), 1619–1631. https://doi.org/10.1021/acs.jmedchem.4c02269

4a.1.23



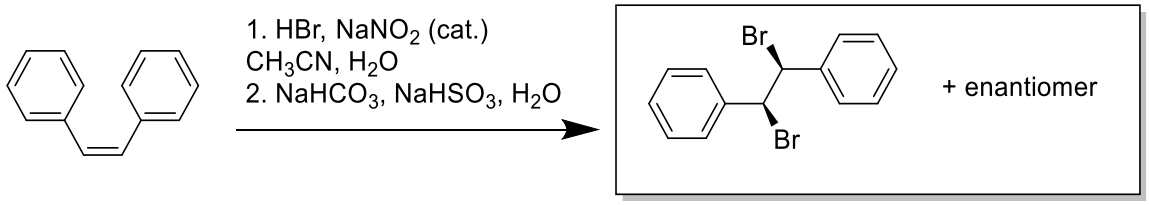
Feng, X.-T.; Min, Q.-Q.; Zhang, S.-Y.; Zhao, H.-Y.; Zhang, X. Difluoromethylene Cyclobutyl Sulfonium Salts: Versatile Reagents for Chemodivergent Synthesis of Difluoroalkylated Cyclobutenes and Cyclobutanes. *Chem. Sci.* 2025, *16* (36), 16552–16558. https://doi.org/10.1039/D5SC05409E

4a.1.24



Mi, Y.; Ren, Y.-H.; Li, Y.; Zhang, R.-C.; Zhao, J.-X.; Zhou, B.; Yue, J.-M. Rare Chlorinated C_{19} Steroids Hocarnoids A and B from *Hoya Carnosa* : Isolation, Semisynthesis, and Anti-Inflammation. *J. Org. Chem.* 2025, *90* (13), 4714–4724. https://doi.org/10.1021/acs.joc.5c00211

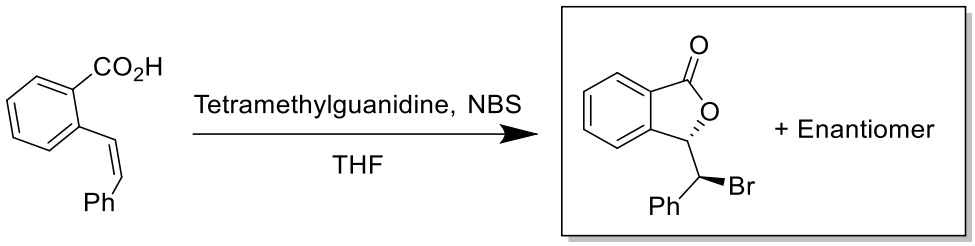
4a.1.25



Note: NO_2^- oxidizes Br^- to yield molecular bromine (Br_2).

Podgoršek, A.; Eissen, M.; Fleckenstein, J.; Stavber, S.; Zupan, M.; Iskra, J. Selective Aerobic Oxidative Dibromination of Alkenes with Aqueous HBr and Sodium Nitrite as a Catalyst. *Green Chem.* 2009, *11* (1), 120–126. https://doi.org/10.1039/B814989E

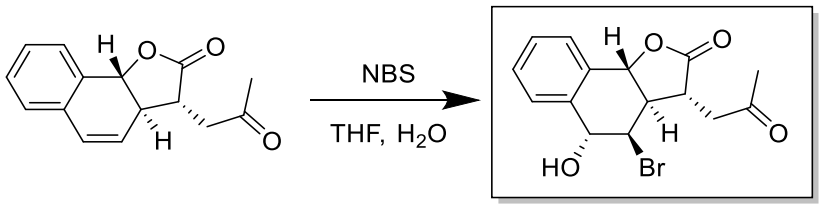
4a.1.26



Note: Tetramethylguanidine is a base

Sugano, M.; Fujiwara, T.; Mochizuki, W.; Inokuma, T.; Yamada, K. Catalyst-Controlled Regioselectivity Switching Inthe Bromolactonization of (*Z*)-StilbenecarboxylicAcids. *Org. Lett.* 2026, *28* (28), 8872–8877. https://doi.org/10.1021/acs.orglett.6c02195

4a.1.27



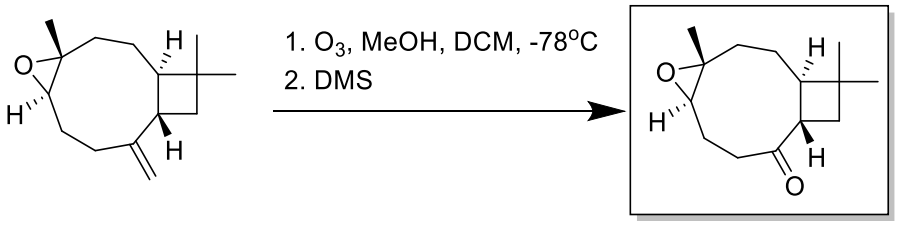
Hint: NBS provides an electrophilic bromine.

Gan, L.; Li, Z.Q.; Chen, T.; Wan, X.; Zhang, J.; Ren, J.; Jiang, M.; Cao, P.; Huang, J.; Deng, Y.H.; Peng, F.; Tian, R.; Wang, Y.; Zhang, Z.; Shao, Z. Highly Cα-Regio-, Enantio- and Diastereoselective Mukaiyama-Type Annulation of Siloxyfurans: Stereodivergent Synthesis of Multi-Stereogenic Tricyclic γ-Lactones. *Chem. Sci*. 2026, *17* (23), 11445-11458. https://doi.org/10.1039/d6sc01491g

Section 4b – Box-Type Questions

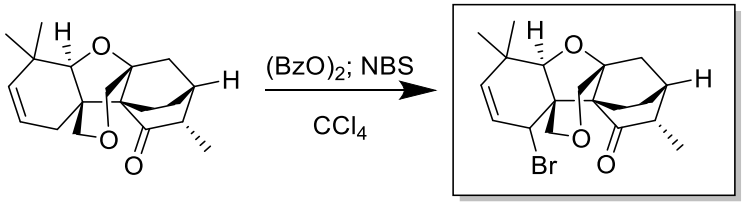
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

4b.1.1



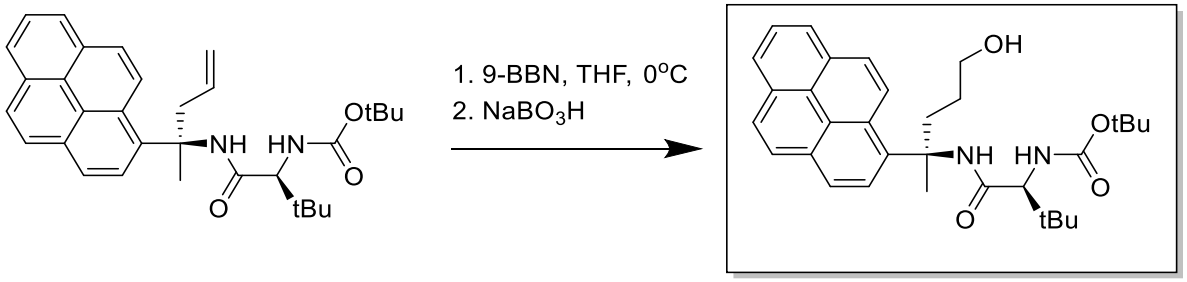
Prout, E. S.; Kwon, O.; Silva, T. G. Regioselective Synthesis of Methyl Enol Ethers from Cycloalkanones via O-Methylation of Kinetic Enolates. *Synthesis* 2026, *58* (13), 1527–1538. https://doi.org/10.1055/a-2822-8676

4b.1.2



Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. Enantioselective Total Synthesis of (−)-Maoecrystal V. *J. Am. Chem. Soc.* 2014, *136* (51), 17750–17756. https://doi.org/10.1021/ja5109694

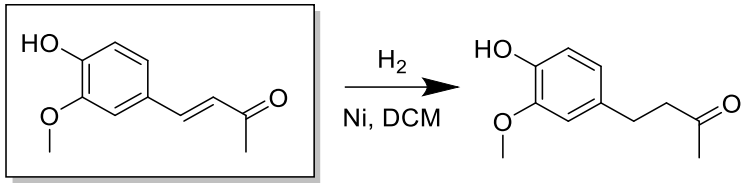
4b.1.3



Note: $NaBO_3H$ (sodium peroxoborate) is O=B-O-O-H (analogous to using $NaOH+H_2O_2$)

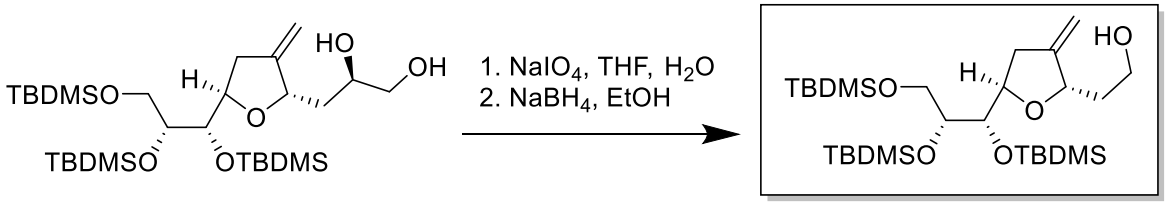
Adrianov, T.; Jacobsen, E. N. Chiral Hydrogen-Bond Donor and Gold(I) Cocatalysis Enables Enantioselective Dearomative Spirocyclization of Naphthols. *J. Am. Chem. Soc.* 2025, *147* (45), 41229–41236. https://doi.org/10.1021/jacs.5c15891

4b.1.4



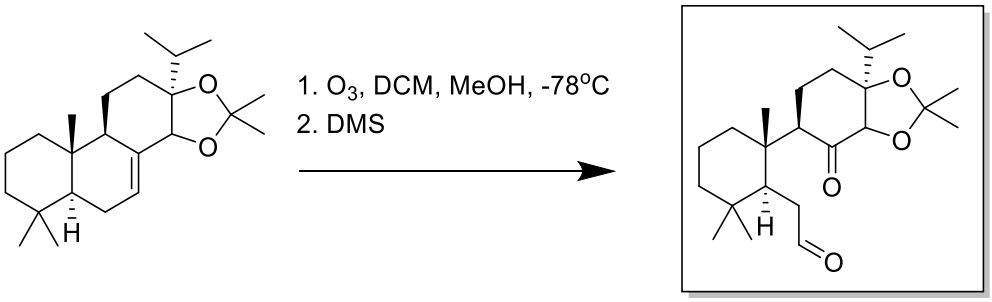
Zhang, Y.; Fayad, E.; Katouah, H. A.; Qin, H.-L. Solvent-Controlled and Highly Chemoselective Reduction of α,β-Unsaturated Ketones and Aldehydes. *J. Org. Chem.* 2025, *90* (16), 5704–5709. https://doi.org/10.1021/acs.joc.5c00151

4b.1.5



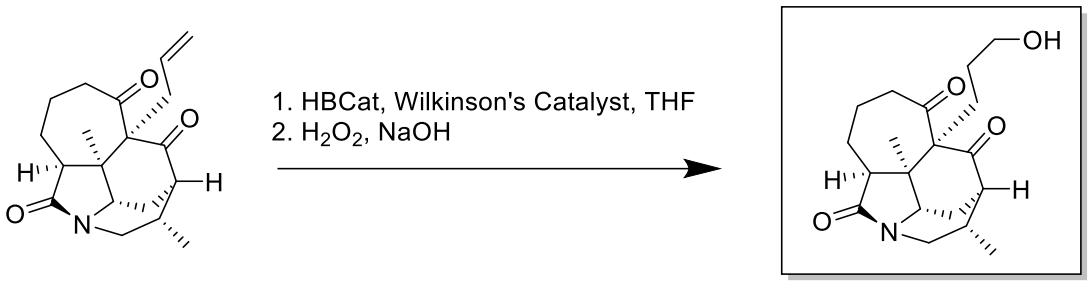
Romiti, F.; Decultot, L.; Clark, J. S. Convergent Synthesis of the C1–C29 Framework of Amphidinolide F. *J. Org. Chem.* 2022, *87* (12), 8126–8141. https://doi.org/10.1021/acs.joc.2c00850

4b.1.6



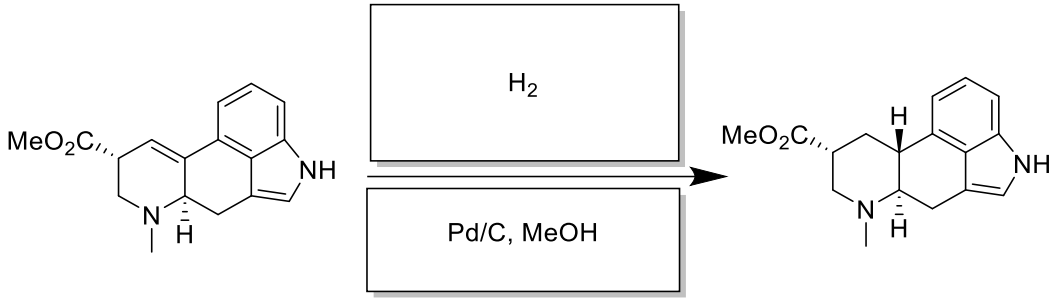
Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. Enantioselective Total Synthesis of Cytotoxic Taiwaniaquinones A and F. *Chem. Commun.* 2010, *46* (48), 9244. https://doi.org/10.1039/c0cc03763j

4b.1.7



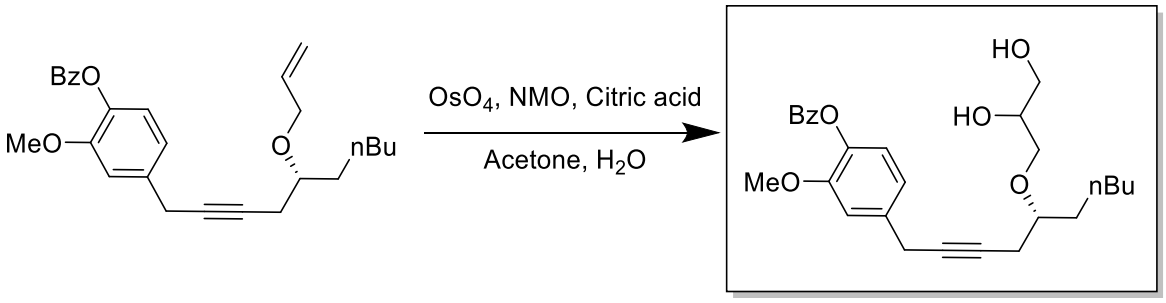
Zhang, Y.; Chen, Y.; Xu, J. Total Synthesis of Daphniphyllum Alkaloids: (+)-Daphlongamine E, (+)-Calyciphylline R, and (–)-10-Deoxydaphnipaxianine A. *Synthesis* 2024, *56* (08), 1273–1284. https://doi.org/10.1055/a-2244-1600

4b.1.8



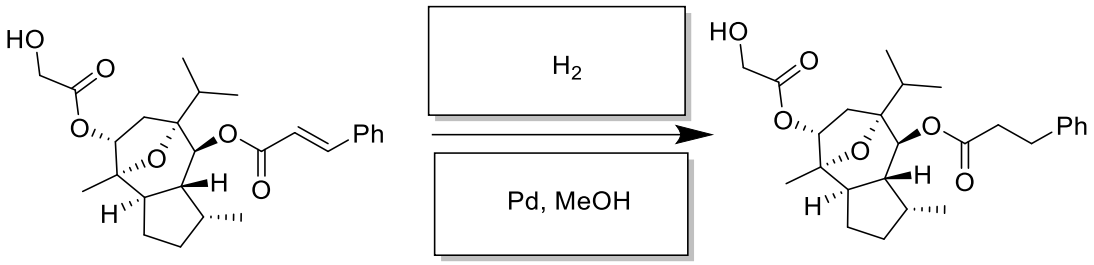
Monerris Mascaro, M.; Henderson, A. P.; Drozdowska, M.; Richardson, R.; Nagel-Savage, D.; Hall, M. J.; Longcake, A.; Mardiana, L.; Golding, B. T. Total Synthesis of 8-Hydroxy-Dihydroergotamine, the Major Human Metabolite of Dihydroergotamine. *Molecules* 2026, *31* (9), 1547. https://doi.org/10.3390/molecules31091547

4b.1.9



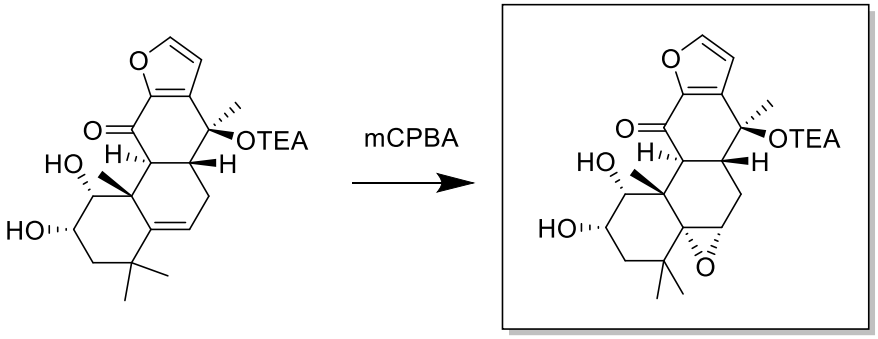
Shet, M. N.; Ramana, C. V. Total Synthesis of (−) and (+)-Zingibergingerols A. *J. Org. Chem.* 2024, *89* (22), 16923–16928. https://doi.org/10.1021/acs.joc.4c01649

4b.1.10



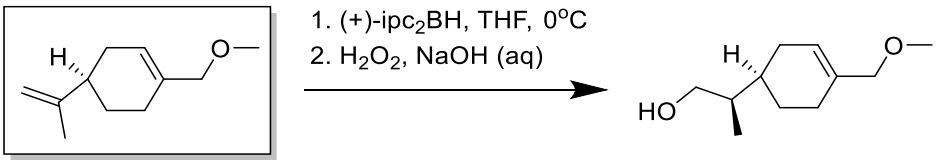
Nicolaou, K. C.; Kang, Q.; Ng, S. Y.; Chen, D. Y.-K. Total Synthesis of Englerin A. *J. Am. Chem. Soc.* 2010, *132* (23), 8219–8222. https://doi.org/10.1021/ja102927n

4b.1.11



Papidocha, S. M.; Bulthaupt, H. H.; Carreira, E. M. Synthesis of Neocaesalpin A, AA, and Nominal Neocaesalpin K**. *Angew. Chem. Int. Ed.* 2023, *62* (48), e202310149. https://doi.org/10.1002/anie.202310149

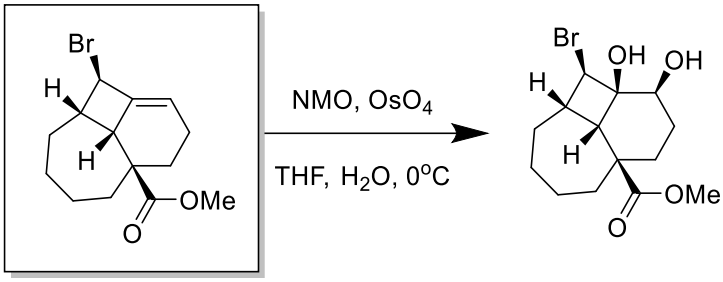
4b.1.12



Note: (+)-ipc$_2$BH (diisopinocampheylborane) is a bulky and chiral hydroboration reagent.

Kuwabara, M.; Matsuo, A.; Kamo, S.; Matsuzawa, A.; Sugita, K. Stereoselective Convergent Synthesis of Carbon Skeleton of Cotylenin A Aglycone. *Synthesis* 2021, *53* (12), 2092–2102. https://doi.org/10.1055/s-0040-1706684

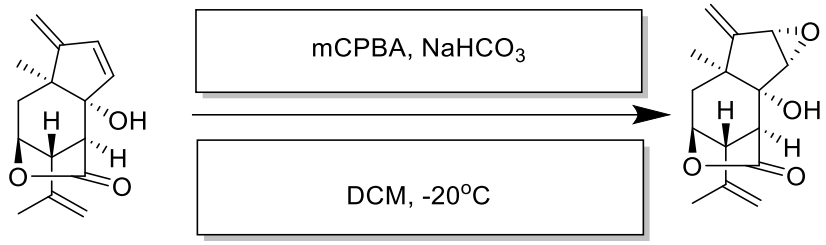
4b.1.13



(Only this stereoisomer is made.)

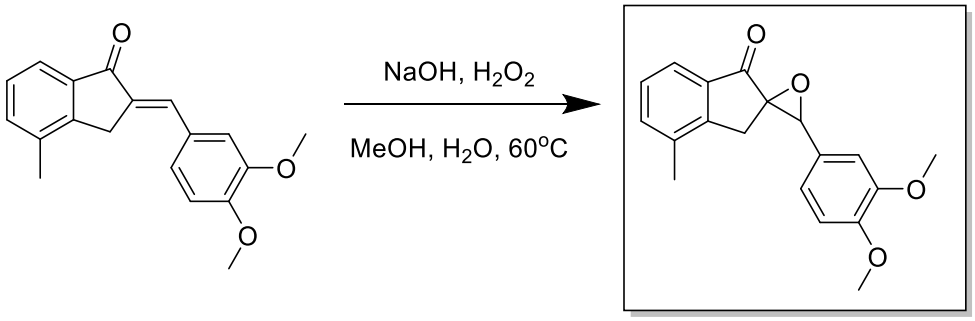
Cao, S.-Y.; Yue, H.-J.; Zhu, M.-Q.; Xu, L. Synthesis of Tricyclo[7.2.1.0^{9,10}]Dodecan-11-One Core Ring Systems of Norditerpenoid Alkaloids and Racemulosine. *Org. Chem. Front.* 2020, *7* (7), 933–937. https://doi.org/10.1039/D0QO00088D

4b.1.14



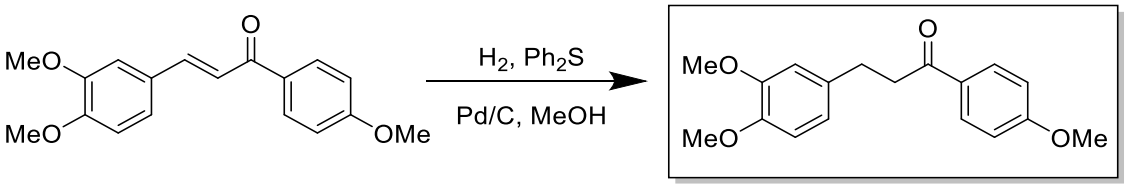
Kuwabara, M.; Matsuo, A.; Kamo, S.; Matsuzawa, A.; Sugita, K. Stereoselective Convergent Synthesis of Carbon Skeleton of Cotylenin A Aglycone. *Synthesis* 2021, *53* (12), 2092–2102. https://doi.org/10.1055/s-0040-1706684

4b.1.15



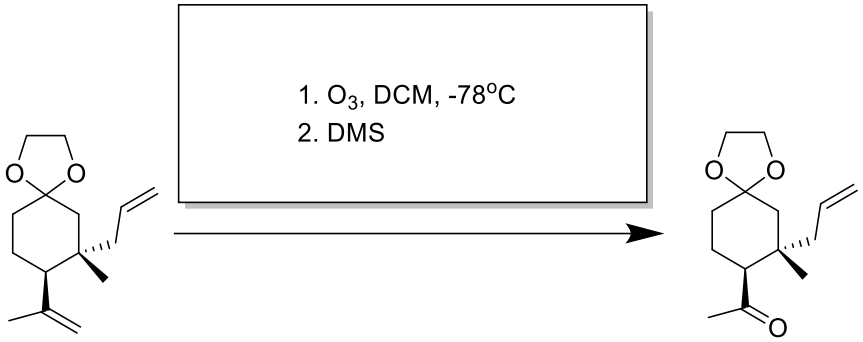
Story, J. B.; Ringler, K. E.; Nguyen, C. L.; Drance, M. J.; Howard, E. M. Synthesis of 2-Naphthols via a Trifluoroacetic Acid-Mediated Epoxy Alcohol Rearrangement. *J. Org. Chem.* 2026, *91* (14), 5249–5254. https://doi.org/10.1021/acs.joc.6c00021

4b.1.16



Deka, U.; Gogoi, A.; Das, S. K. Reactivity Divergence in the Cyclization of Terminal Epoxides All-Carbon-Tethered to Indoles. *Chem. Commun.* 2026, *62* (7), 2222–2225. https://doi.org/10.1039/D5CC06074E

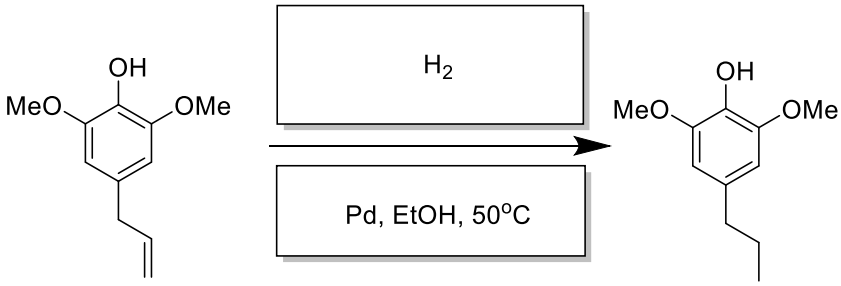
4b.1.17



Note: For introductory organic chemistry courses, you typically do not need to know why this reaction occurred only on the specific functional group.

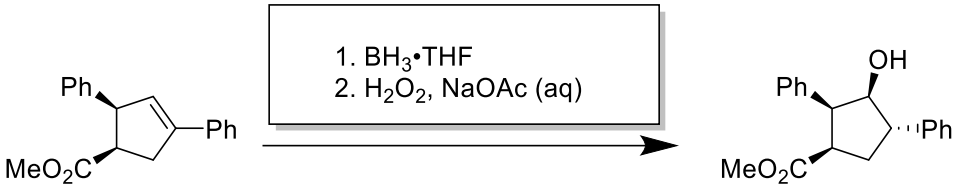
Sreelekshmi, S.; Kaliappan, K. P. A Unified Strategy to the Enantiomers of Atractylenolides and Related Eudesmane Sesquiterpenoids from (−)-Verbenone. *Org. Biomol. Chem.* 2026, *24* (32), 6564–6570. https://doi.org/10.1039/D6OB01041E

4b.1.18



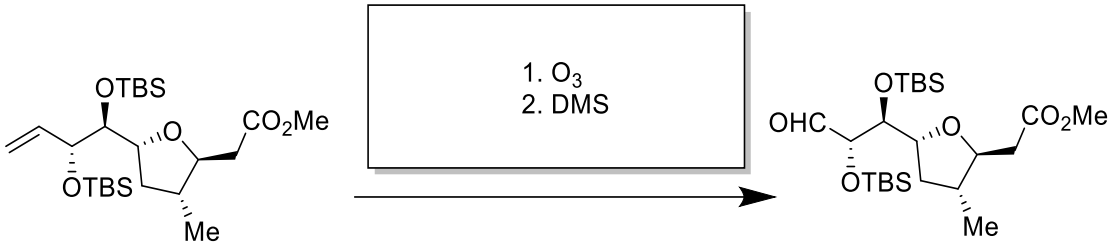
Li, X.; Chavez, A. J.; Zhang, H.; Andryushkina, D.; Ford, P. C.; Abu-Omar, M. M. Selective Conversion of Lignin to Benzoquinones under Ambient Conditions: Unlocking the Potential of a Single Platform Chemical Strategy. *Green Chem.* 2026, *28* (9), 4255–4262. https://doi.org/10.1039/D5GC04121J

4b.1.19



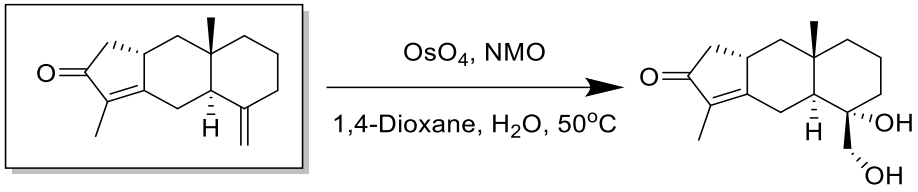
Zhao, J.; He, L.; Lv, H. Enantioselective Synthesis of Chiral Cyclopentenes by Relay Catalysis from Terminal Alkynes, Enones, and Syngas. *Org. Lett.* 2026, *28* (1), 202–207. https://doi.org/10.1021/acs.orglett.5c04598

4b.1.20



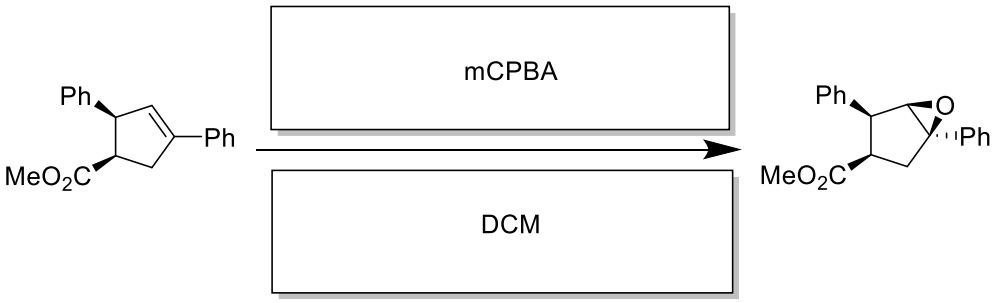
Ciss, I.; Seck, M.; Figadère, B.; Ferrié, L. Advances Toward Amphidinolides C, F and U: Isolations, Synthetic Studies and Total Syntheses. *Chem. Eur. J.* 2024, *30* (27), e202400471. https://doi.org/10.1002/chem.202400471

4b.1.21



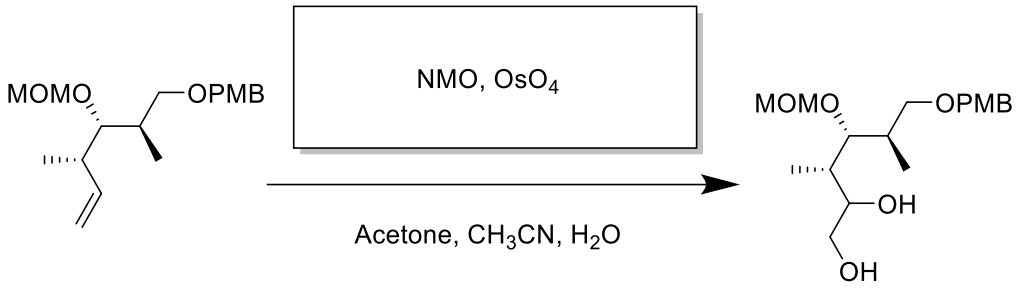
Sreelekshmi, S.; Kaliappan, K. P. A Unified Strategy to the Enantiomers of Atractylenolides and Related Eudesmane Sesquiterpenoids from (−)-Verbenone. *Org. Biomol. Chem.* 2026, *24* (32), 6564–6570. https://doi.org/10.1039/D6OB01041E

4b.1.22



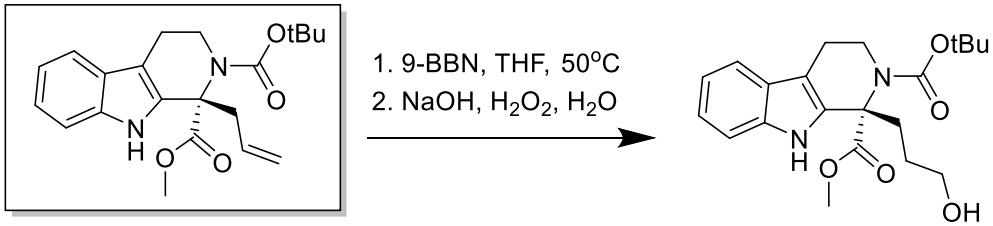
Zhao, J.; He, L.; Lv, H. Enantioselective Synthesis of Chiral Cyclopentenes by Relay Catalysis from Terminal Alkynes, Enones, and Syngas. *Org. Lett.* 2026, *28* (1), 202–207. https://doi.org/10.1021/acs.orglett.5c04598

4b.1.23



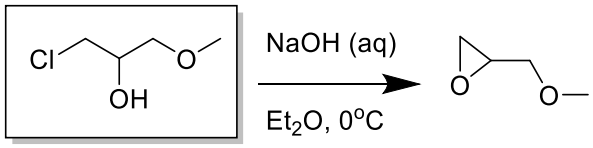
Sennari, G.; Watanabe, A.; Ōno, T.; Oshita, J.; Noguchi, Y.; Hirose, T.; Sunazuka, T. Macrocyclic Skeletal Modification Approach to the Anti-Trypanosomal Macrolides, Actinoallolides. *Chem. Commun.* 2025, *61* (56), 10367–10370. https://doi.org/10.1039/D5CC01915J

4b.1.24



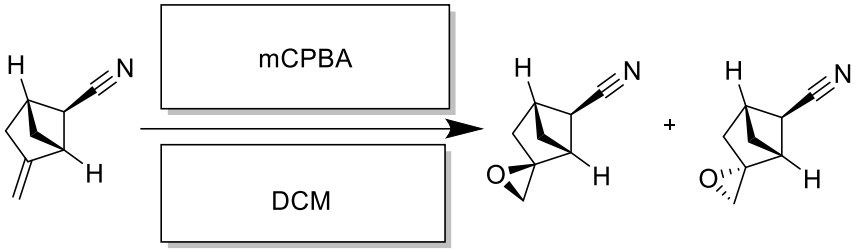
Wang, Z.; Chen, D.; Chang, J.; Li, Y.; Su, Y.; Tang, P.; Chen, F.-E. Enantioselective Synthesis of Functionalized 2,2-Disubstituted Piperidines Enabled by Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation. *Org. Lett.* 2026, *28* (2), 794–799. https://doi.org/10.1021/acs.orglett.5c04932

4b.1.25



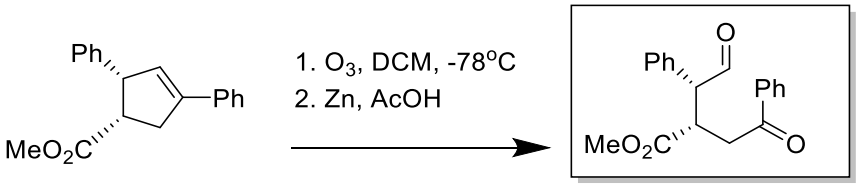
Mironov, V. F.; Nemtarev, A. V.; Tsepaeva, O. V.; Dimukhametov, M. N.; Litvinov, I. A.; Voloshina, A. D.; Pashirova, T. N.; Titov, E. A.; Lyubina, A. P.; Amerhanova, S. K.; Gubaidullin, A. T.; Islamov, D. R. Rational Design 2-Hydroxypropylphosphonium Salts as Cancer Cell Mitochondria-Targeted Vectors: Synthesis, Structure, and Biological Properties. *Molecules* 2021, *26* (21), 6350. https://doi.org/10.3390/molecules26216350

4b.1.26



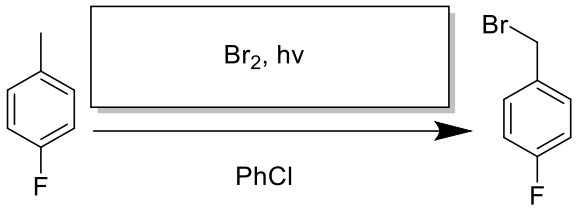
Mehta, G.; Singh, S. R.; Balanarayan, P.; Gadre, S. R. Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]Hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects. *Org. Lett.* 2002, *4* (14), 2297–2300. https://doi.org/10.1021/ol026005d

4b.1.27



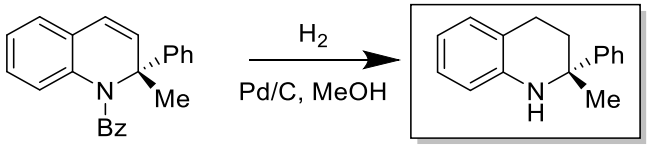
Zhao, J.; He, L.; Lv, H. Enantioselective Synthesis of Chiral Cyclopentenes by Relay Catalysis from Terminal Alkynes, Enones, and Syngas. *Org. Lett.* 2026, *28* (1), 202–207. https://doi.org/10.1021/acs.orglett.5c04598

4b.1.28



Steiner, A.; Williams, J. D.; De Frutos, O.; Rincón, J. A.; Mateos, C.; Kappe, C. O. Continuous Photochemical Benzylic Bromination Using *in Situ* Generated Br_2 : Process Intensification towards Optimal PMI and Throughput. *Green Chem.* 2020, *22* (2), 448–454. https://doi.org/10.1039/C9GC03662H

4b.1.29



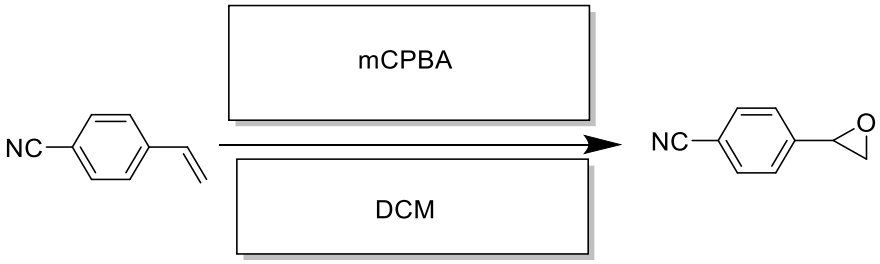
Huang, W.-J.; Chen, J.; Bai, Y.-Q.; Zhou, Y.-G.; Jiang, G.-F.; Wu, B. Asymmetric Synthesis of 2,2-Disubstituted Dihydroquinolines via Rhodium-Catalyzed Dearomative Arylation and Alkenylation of 2-Substituted Quinolinium Salts. *Org. Lett.* 2026, *28* (7), 2284–2288. https://doi.org/10.1021/acs.orglett.5c05303

4b.1.30



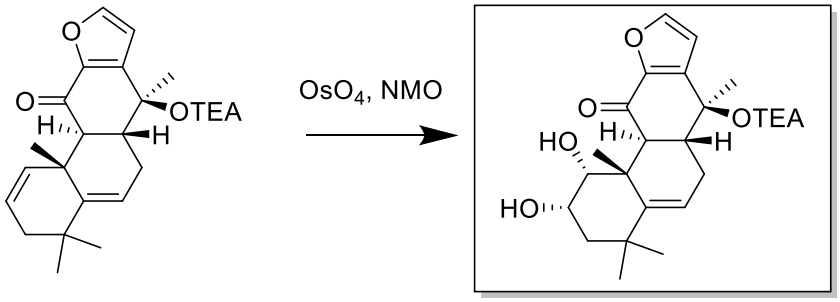
Mehta, G.; Singh, S. R.; Balanarayan, P.; Gadre, S. R. Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]Hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects. *Org. Lett.* 2002, *4* (14), 2297–2300. https://doi.org/10.1021/ol026005d

4b.1.31



Qin, L.; Li, M.; Wang, X.; You, C.; Deng, G.; Chen, Y. Engineering of $P450_{PL2}$ Monooxygenase for the Stereoselective Synthesis of (*R*)-Styrene Oxides. *Org. Lett.* 2026, *28* (8), 2567–2572. https://doi.org/10.1021/acs.orglett.5c05206

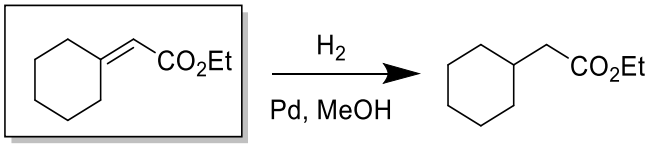
4b.1.32



Hint: The trisubstituted alkene is not accessible by the reagents.

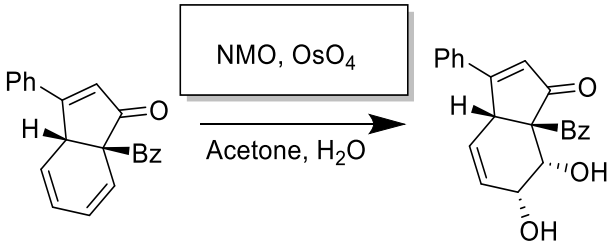
Papidocha, S. M.; Bulthaupt, H. H.; Carreira, E. M. Synthesis of Neocaesalpin A, AA, and Nominal Neocaesalpin K**. *Angew. Chem. Int. Ed.* 2023, *62* (48), e202310149. https://doi.org/10.1002/anie.202310149

4b.1.33



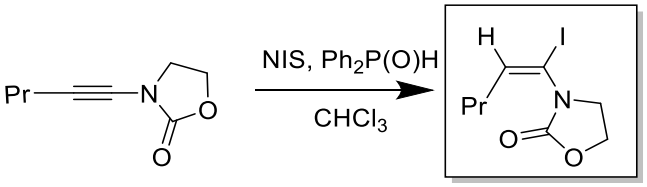
Golubev, V.; Phan, N. H. T.; Pohl, R.; Tarabek, J.; Císařová, I.; Jahn, U. A Synthetic Approach to Sterically Hindered P-Chiral Phosphine Ligands and Their Applications for Asymmetric Gold Catalysis. *Adv. Synth. Catal.* 2026, *368* (1), e70067. https://doi.org/10.1002/adsc.70067

4b.1.34



Lu, J.; Dong, H.; Wu, S.; Wang, C.; Lin, A.; Sun, P. Enantioselective Synthesis of Bicyclo[4.3.0]Nonatrienones via Palladium-Catalyzed Desymmetric 1,5-Enyne Cycloisomerization. *Org. Lett.* 2026, *28* (5), 1826–1831. https://doi.org/10.1021/acs.orglett.5c05377

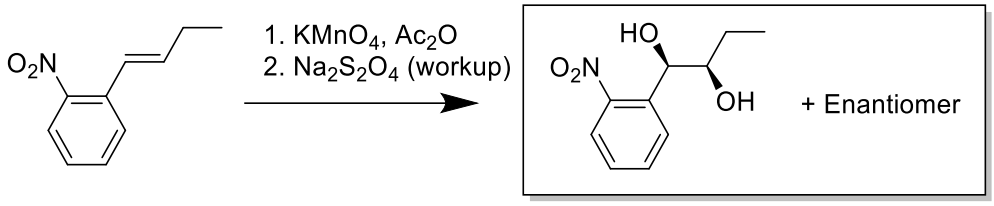
4b.1.35



Note: NIS is an iodine version of NBS. For introductory organic chemistry courses, you can ignore the use of $Ph_2P(O)H$.

Pati, S. S.; Mishra, A.; Das, J. P. Construction of Acyclic Vicinal All-Carbon Quaternary and Tertiary Carbon Stereocenters via a Stereoselective Claisen Rearrangement. *Org. Lett.* 2025, *27* (35), 9681-9686. https://doi.org/10.1021/acs.orglett.5c02876

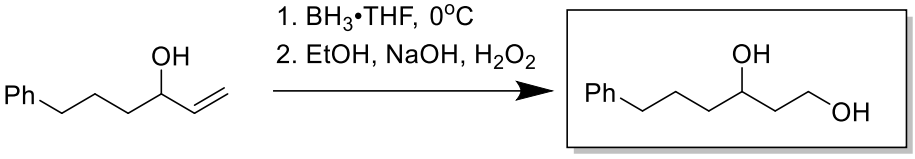
4b.1.36



Note: Sodium dithionite ($Na_2S_2O_4$) is a reducing agent that decomposes permanganate.

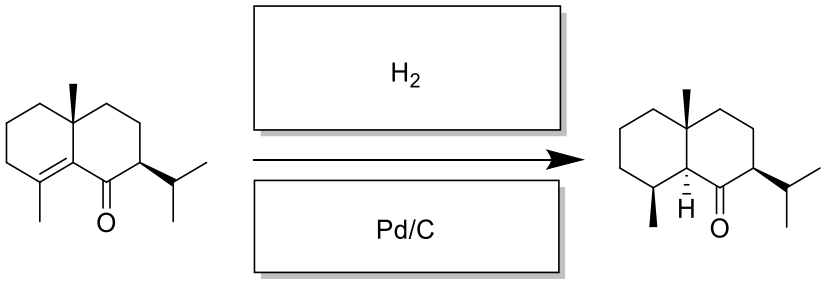
Racochote, S.; Nutthawasutha, C.; Bado, U.; Theppitak, C.; Tummatorn, J.; Ruchirawat, S.; Thongsornkleeb, C. Photoisomerization of Isatogens to Benzoxazin-4-Ones. *J. Org. Chem.* 2026, acs.joc.6c00639. https://doi.org/10.1021/acs.joc.6c00639

4b.1.37



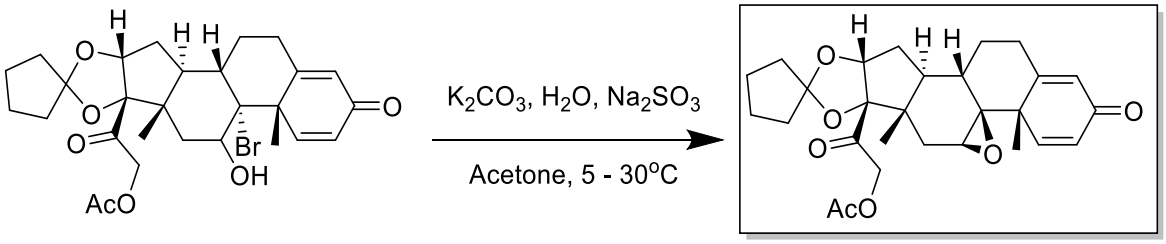
Liu, Z.; Breit, B. Rhodium-Catalyzed Regioselective Addition of *N* -Hydroxyl Imides to Internal Alkynes. *Isr. J. Chem.* 2026, *66* (3), e70014. https://doi.org/10.1002/ijch.70014

4b.1.38



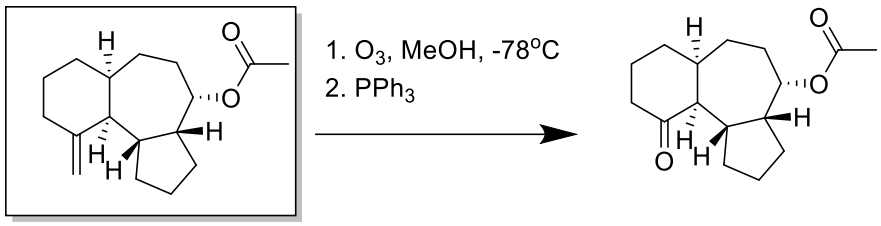
Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* 2009, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

4b.1.39



Kharpe, A. A.; Wagare, D. S.; Mokale, S.; Netankar, P. D. An Efficient Protocol for the Synthesis of Amcinonide from Tetraene Acetate. *Polycyclic Aromat. Compd.* 2025, *45* (7), 1367–1379. https://doi.org/10.1080/10406638.2025.2454256

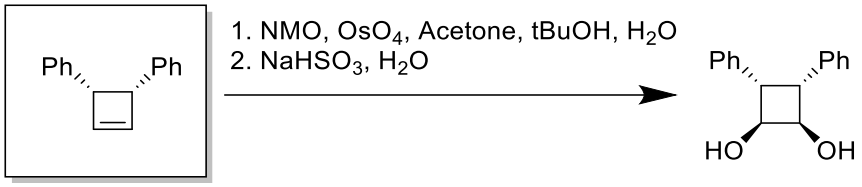
4b.1.40



Note: PPh_3 is a reducing agent analogous to DMS

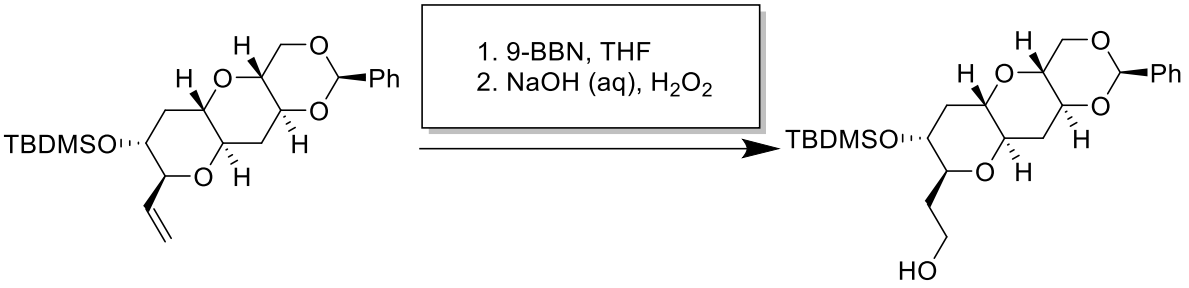
Wang, Z.; Zhang, Z.; Xie, X.; Qin, S.; Fu, S.; Liu, B. Construction of the Tricyclic Core of Rhamnofolane-Type Diterpenoids. *Org. Chem. Front.* 2026, *13* (5), 1617–1624. https://doi.org/10.1039/D5QO01699A

4b.1.41



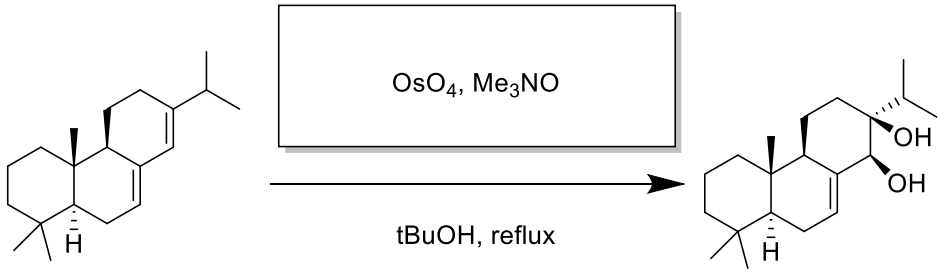
Zhao, R.; Zhou, D.-Y.; Asano, K.; Suzuki, T.; Suzuki, T. Stereodefined Synthesis of Acyclic *Meso* -2,3-Diaryl Dialdehydes and Their Iridium-Catalyzed Enantioselective Desymmetrization. *J. Org. Chem.* 2026, *91* (30), 10461–10465. https://doi.org/10.1021/acs.joc.6c00927

4b.1.42



Moya-Utrera, F.; Cheng-Sánchez, I.; Fuentes-Pino, I.; Sánchez-Ruiz, A.; Sarabia, F. Efficient Synthesis of Fused Polycyclic Ether Systems via Sulfonium Ylides: A Synthetic Approach to Yessotoxin and Adriatoxin. *Marine Drugs* 2025, *23* (2), 51. https://doi.org/10.3390/md23020051

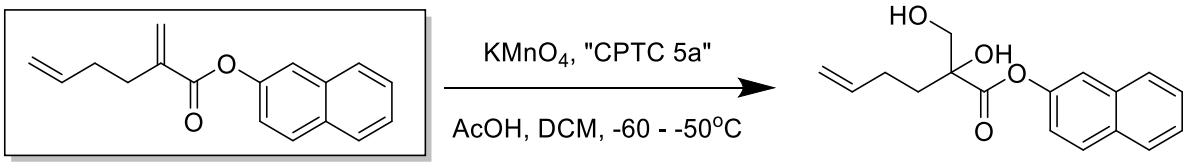
4b.1.43



Note: Me_3NO (trimethylamine N-oxide) is analogous to NMO.

Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. Enantioselective Total Synthesis of Cytotoxic Taiwaniaquinones A and F. *Chem. Commun.* 2010, *46* (48), 9244. https://doi.org/10.1039/c0cc03763j

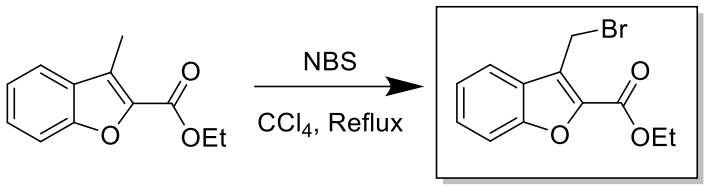
4b.1.44



Note: For introductory organic chemistry courses, you can ignore the catalyst CPTC 5a.

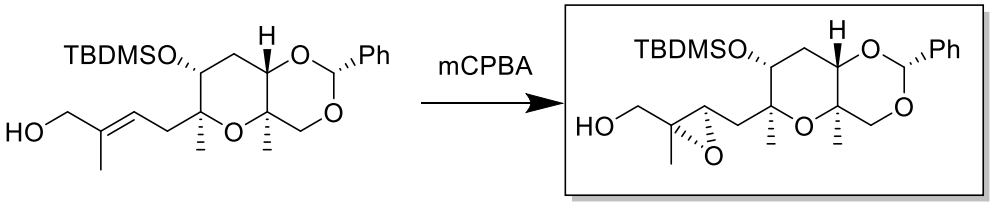
Rank, N. S.; Hussein, A. A.; Cecil, A. L.; Light, M. E.; Brown, R. C. D. Enantioselective Synthesis of Tetrahydrofurans by Permanganate-Mediated Oxidative Cyclisation of 1,5-Dienes Using Chiral Phase-Transfer Catalysis. *Org. Chem. Front.* 2026, *13* (13), 4078–4088. https://doi.org/10.1039/D6QO00377J

4b.1.45



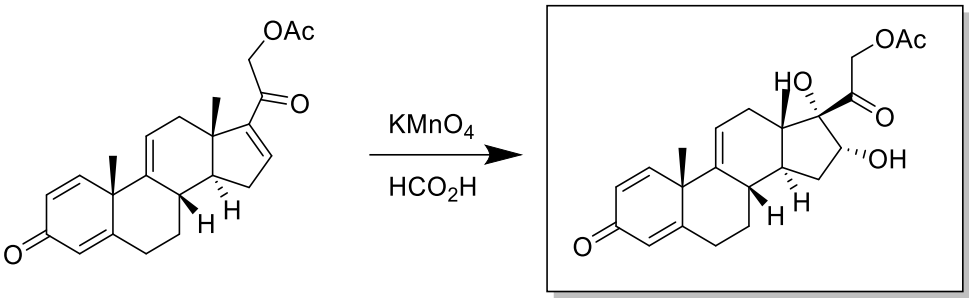
Eldehna, W. M.; Tawfik, H. O.; Nafie, M. S.; Al Kamaly, O.; El-Hamaky, A. A.; El Hassab, M. A.; Elsayed, Z. M.; Elnaggar, Y. S. R.; Al-Karmalawy, A. A.; Di Giacomo, V.; Balaha, M. Novel Benzofuran-Conjugated Indolin-2-Ones as Anticancer Agents: Design, Synthesis, Biological Assessments, and Molecular Modeling Insights. *Bioorg. Chem.* 2025, *160*, 108494. https://doi.org/10.1016/j.bioorg.2025.108494

4b.1.46



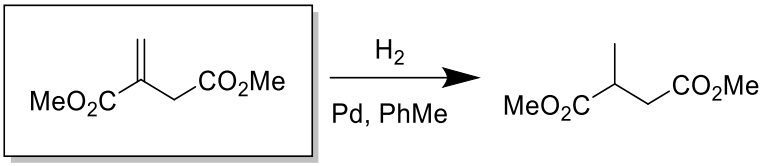
Moya-Utrera, F.; Cheng-Sánchez, I.; Fuentes-Pino, I.; Sánchez-Ruiz, A.; Sarabia, F. Efficient Synthesis of Fused Polycyclic Ether Systems via Sulfonium Ylides: A Synthetic Approach to Yessotoxin and Adriatoxin. *Marine Drugs* 2025, *23* (2), 51. https://doi.org/10.3390/md23020051

4b.1.47



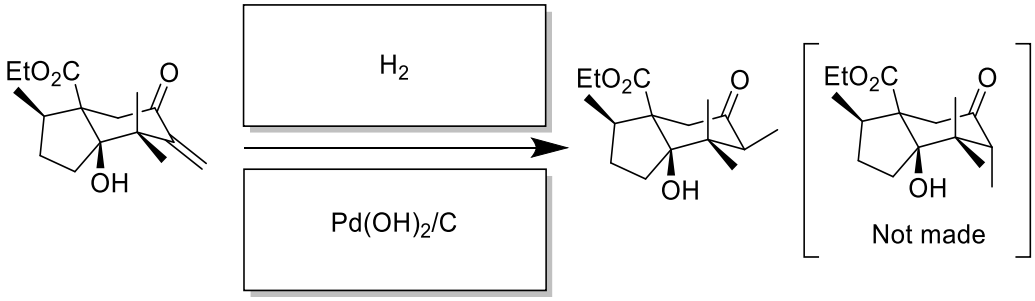
Kharpe, A. A.; Wagare, D. S.; Mokale, S.; Netankar, P. D. An Efficient Protocol for the Synthesis of Amcinonide from Tetraene Acetate. *Polycyclic Aromat. Compd.* 2025, *45* (7), 1367–1379. https://doi.org/10.1080/10406638.2025.2454256

4b.1.48



Golubev, V.; Phan, N. H. T.; Pohl, R.; Tarabek, J.; Císařová, I.; Jahn, U. A Synthetic Approach to Sterically Hindered P-Chiral Phosphine Ligands and Their Applications for Asymmetric Gold Catalysis. *Adv. Synth. Catal.* 2026, *368* (1), e70067. https://doi.org/10.1002/adsc.70067

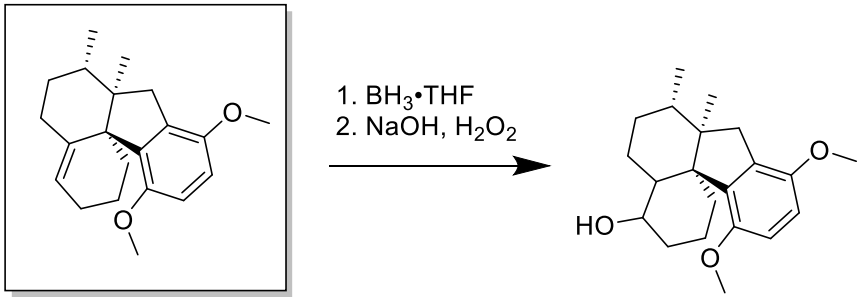
4b.1.49



Explain why after hydrogenation and then base, only the specific stereoisomer is made.

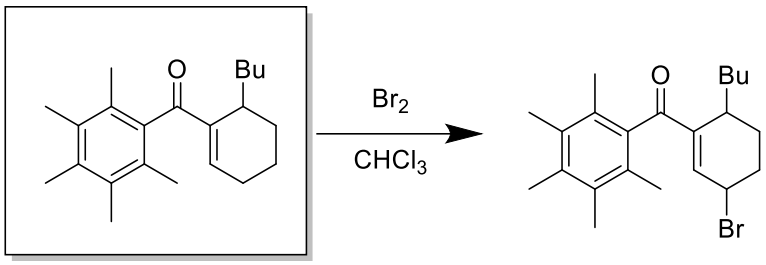
Fu, P.; Liu, T.; Shen, Y.; Lei, X.; Xiao, T.; Chen, P.; Qiu, D.; Wang, Z.; Zhang, Y. Divergent Total Syntheses of *Illicium* Sesquiterpenes through Late-Stage Skeletal Reorganization. *J. Am. Chem. Soc.* 2023, *145* (33), 18642–18648. https://doi.org/10.1021/jacs.3c06442

4b.1.50



Chong, C.; Chang, L.; Grimm, I.; Zhang, Q.; Kuang, Y.; Wang, B.; Kang, J.; Liu, W.; Baars, J.; Guo, Y.; Schmalz, H.-G.; Lu, Z. Divergent Total Synthesis of the Revised Structures of Marine Anti-Cancer Meroterpenoids (+)-Dysiherbols A-E. *Chem. Sci.* 2023. *14* (12). 3302-3310. https://doi.org/10.1039/d3sc00173c

4b.1.51

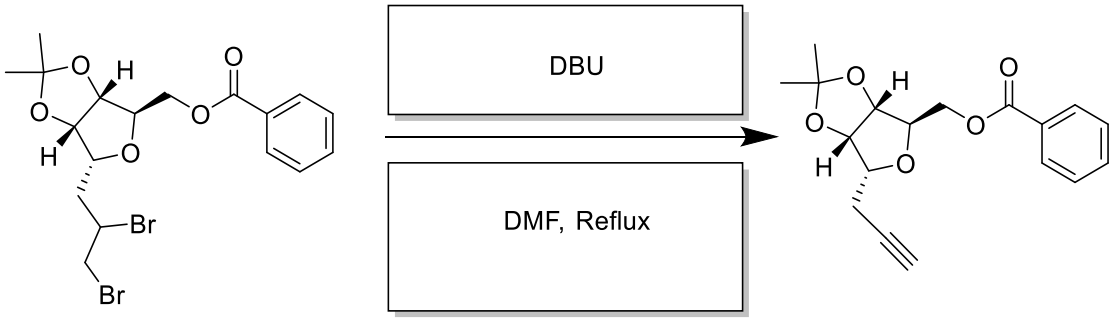


Amer, M. M.; Hou, J.; Wang, J.; Mazeikaite, A.; Donohoe, T. J. Asymmetric Hydride Shift Reactions Catalyzed by Chiral Aluminium Complexes. *Angew. Chem. Int. Ed.* 2026, *65* (5), e202521374. https://doi.org/10.1002/anie.202521374

Section 5 – Box-Type Questions

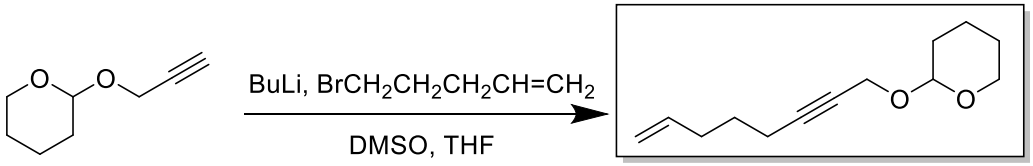
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

5.1.1



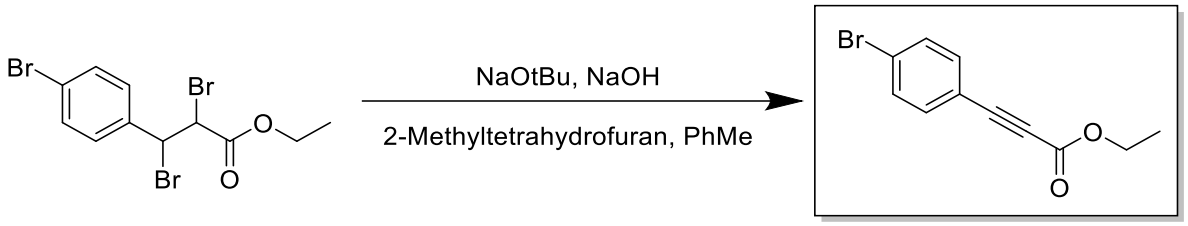
González-Márquez, V.; Cruz-Gregorio, S.; Sandoval-Lira, J.; Quintero, L.; Sartillo-Piscil, F. Total Synthesis of the Proposed Structure of Decurrenside D. *Tetrahedron Lett.* 2015, *56* (40), 5416-5418. https://doi.org/10.1016/j.tetlet.2015.08.003

5.1.2



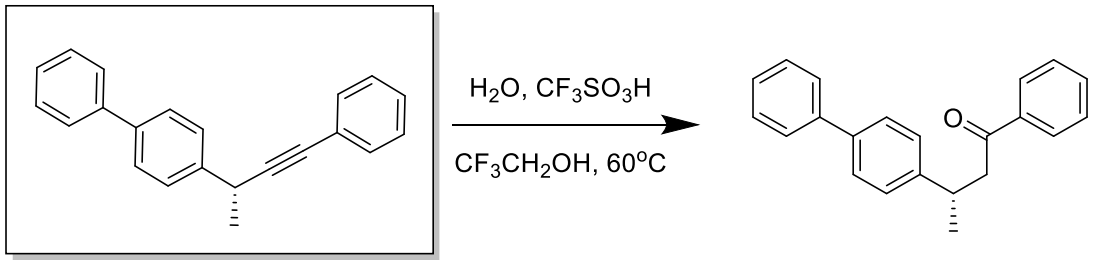
Yuan, W.-H.; Hu, Y.; Wang, X.-H.; Chen, Z.-C.; Du, W.; Chen, Y.-C. Nickel-Catalyzed Asymmetric Reductive Allenylation of Aldehydes with Propargyl Carbonates. *Org. Lett.* 2026, *28* (23), 7338–7342. https://doi.org/10.1021/acs.orglett.6c01807

5.1.3



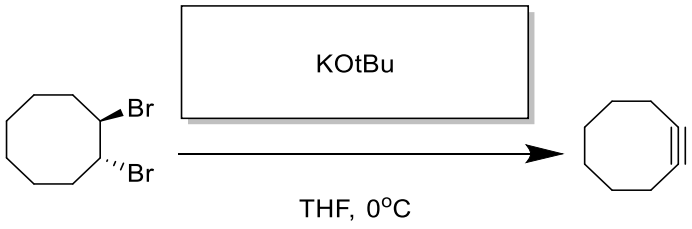
Chen, J.; Chen, T.; Hu, Q.; Püntener, K.; Ren, Y.; She, J.; Du, Z.; Scalone, M. Practical Asymmetric Hydrogenation-Based Synthesis of a Class-Selective Histone Deacetylase Inhibitor. *Org. Process Res. Dev.* 2014, *18* (12), 1702–1713. https://doi.org/10.1021/op500250b

5.1.4



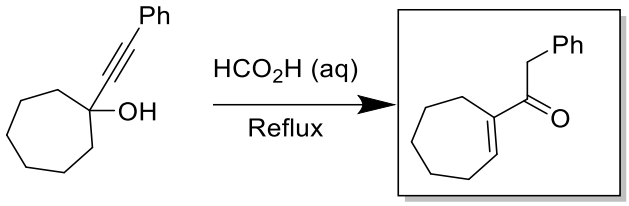
Gao, Z.; Xu, D.-D.; Fan, L.-W.; Luo, Q.; Zhou, Z.-J.; Dong, X.-Y.; Li, Z.-L.; Liu, X.-Y. Copper-Catalyzed Enantioconvergent Radical Deborylative Coupling of Racemic Benzylboronic Esters with Alkynes and Alkenylboronic Esters. *J. Am. Chem. Soc.* 2026, *148* (7), 7655–7662. https://doi.org/10.1021/jacs.5c21668

5.1.5



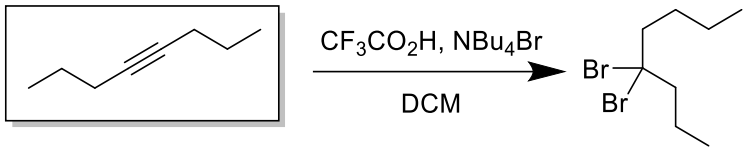
Lu, C.; Zhang, M.; Bai, T.; Yan, Z.; Pu, X.; Huang, X.; Chang, J.; Wang, Z.; Bai, X. Iron-Catalysed 1,4-Reduction of Quinones for the Synthesis of Hydroquinones. *Org. Biomol. Chem.* 2026, *24* (7), 1522–1527. https://doi.org/10.1039/D5OB01911G

5.1.6



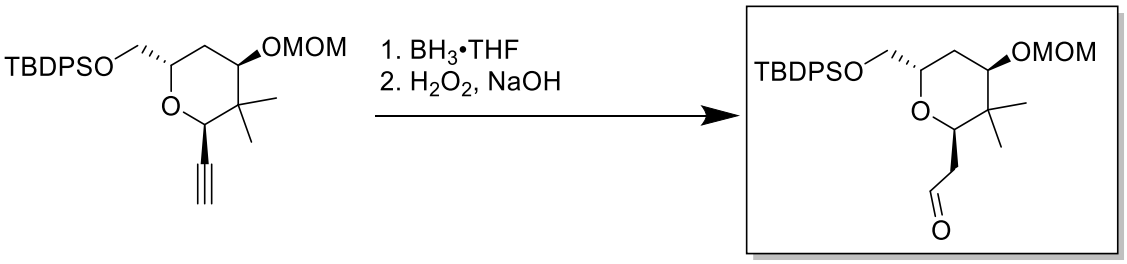
Scarpi, D.; Visi, S.; Muzzu, A.; Occhiato, E. G. One-Pot Gold(I)-Catalyzed Rautenstrauch Rearrangement/Nitrosocarbonyl Hetero-Diels–Alder Reaction Sequence for the Synthesis of α-Hydroxylated Cyclopentenones. *Eur. J. Org. Chem.* 2026. *29* (27), e70611. https://doi.org/10.1002/ejoc.70611

5.1.7



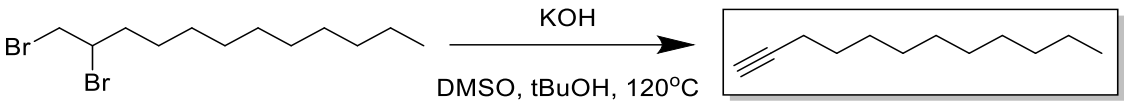
Weiss, H. M.; Touchette, K. M. Bromide Assisted Addition of Hydrogen Bromide to Alkynes and Allenes. *J. Chem. Soc., Perkin Trans. 2.* 1998, No. 6, 1523–1528. https://doi.org/10.1039/a703569a

5.1.8



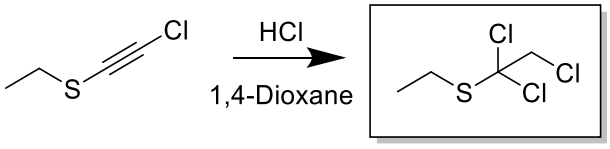
Shangguan, N.; Kiren, S.; Williams, L. J. A Formal Synthesis of Psymberin. *Org. Lett.* 2007, *9* (6), 1093–1096. https://doi.org/10.1021/ol063143k

5.1.9



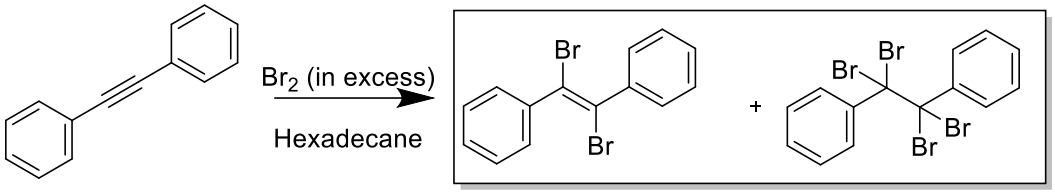
Kumaki, W.; Kinoshita, H.; Miura, K. Regio- and Stereoselective Synthesis of Bromoalkenes by Homolytic Hydrobromination of Alkynes with Hydrogen Bromide. *Tetrahedron* 2022, *110*, 132687. https://doi.org/10.1016/j.tet.2022.132687

5.1.10



D'yachkova, S. G.; Nikitina, E. A.; Gusarova, N. K. (Organylthio)chloroacetylenes: VII. Hydrochlorination of (Alkylthio)chloroacetylenes. *Russ. J. Gen. Chem.* 2003, *73* (8), 1246-1248. https://doi.org/10.1023/B:RUGC.0000007649.71394.73

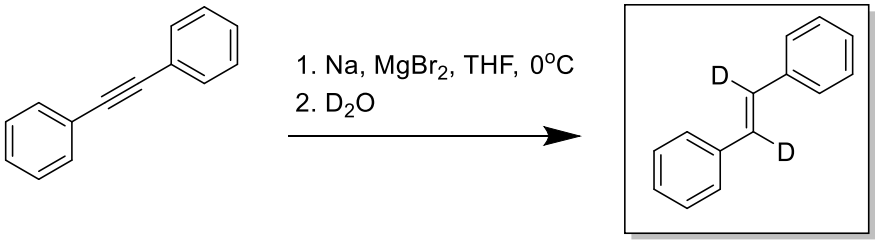
5.1.11



The authors isolated two products, with one in higher quantity than the other.

Ma, K.; Li, S.; Weiss, R. G. Stereoselective Bromination Reactions Using Tridecylmethylphosphonium Tribromide in a "Stacked" Reactor. *Org. Lett.* 2008, *10* (19), 4155–4158.

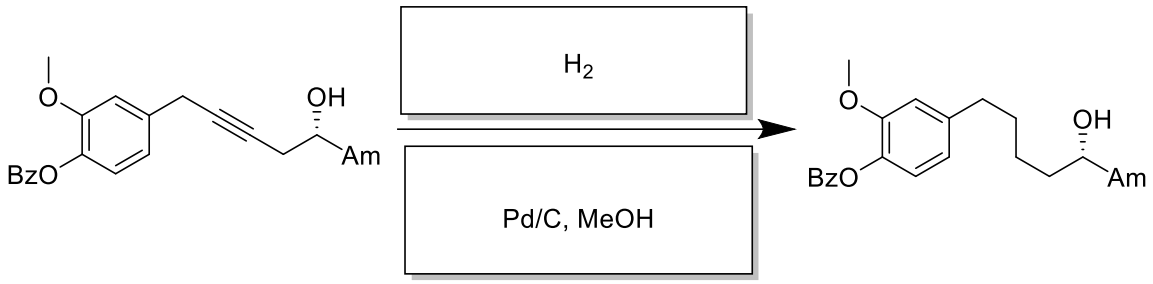
5.1.12



Note: The $MgBr_2$ displaces the Na after the reduction step to stabilize the carbanion.

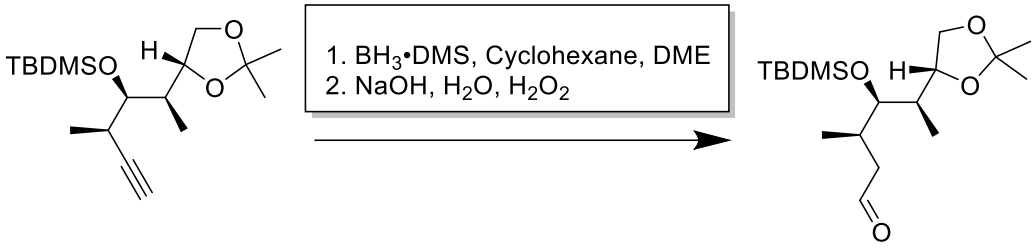
Yamaguchi, H.; Takahashi, F.; Kurogi, T.; Yorimitsu, H. Sodium-Mediated Reductive *anti*-Dimagnesiation of Diarylacetylenes with Magnesium Bromide. *Synthesis* 2024, *56* (21), 3307-3313. https://doi.org/10.1055/a-2326-6416

5.1.13



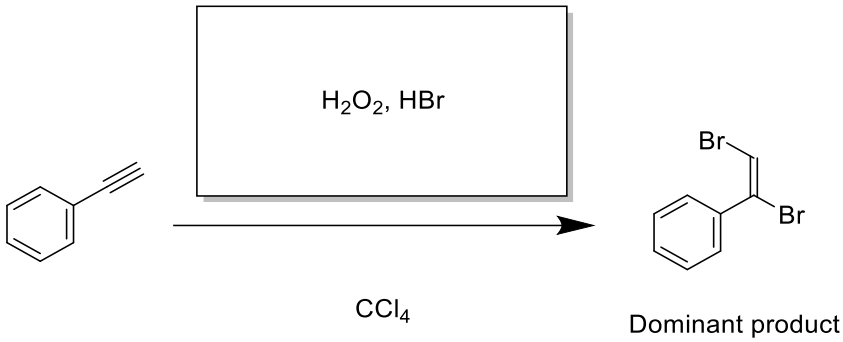
Shet, M. N.; Ramana, C. V. Total Synthesis of (−) and (+)-Zingibergingerols A. *J. Org. Chem.* 2024, *89* (22), 16923–16928. https://doi.org/10.1021/acs.joc.4c01649

5.1.14



Vintonyak, V. V.; Maier, M. E. Synthesis of the Core Structure of Cruentaren A. *Org. Lett.* 2007, *9* (4), 655–658. https://doi.org/10.1021/ol0629317

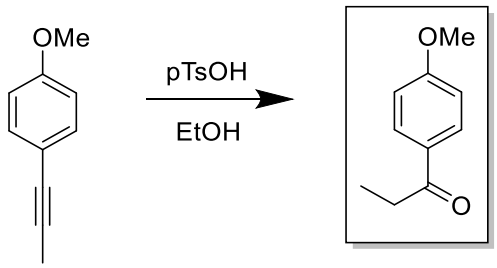
5.1.15



Note: H_2O_2 is an oxidant to convert the bromide to molecular bromine (Br_2).

Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. Simple and Practical Halogenation of Arenes, Alkenes and Alkynes with Hydrohalic Acid/H202 (or TBHP). *Tetrahedron* 1999, *55* (36), 11127-11142. https://doi.org/10.1016/s0040-4020(99)00628-6

5.1.16



Alkahtani, R.; Westphäling, J.; Gorecka, A.; Babaahmadi, R.; Gieman, H.; Finance, M.; Lorente-Martinez, J.; Bhattacherjee, D.; Melen, R. L.; Baik, M.-H.; Wirth, T. Oxidative Rearrangement of Alkynes to Chiral α-Arylalkanoic Esters. *Chem. Sci.* 2026, *17* (2), 1318–1324. https://doi.org/10.1039/D5SC07882B

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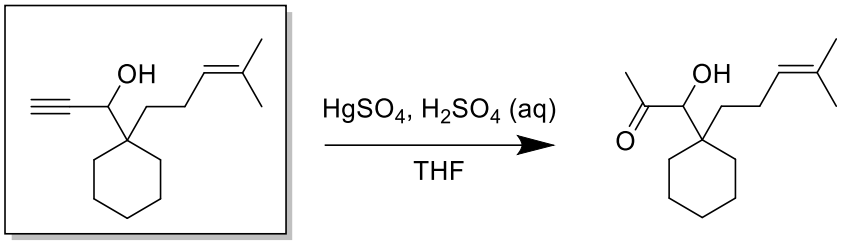
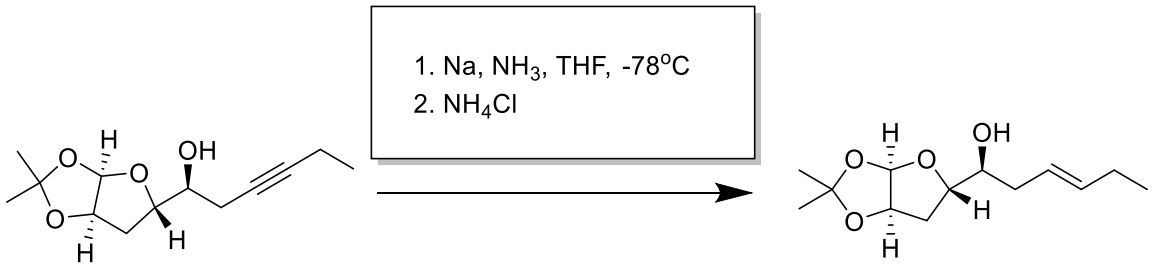


Vulovic, B.; Trmcic, M.; Matovic, R.; Saicic, R. N. Cyclization Reactions of Oxyallyl Cation. A Method for Cyclopentane Ring Formation. *Org. Lett.* 2019, *21* (23), 9618–9621. https://doi.org/10.1021/acs.orglett.9b03791

5.1.18



Senapati, S.; Unmesh, N. A.; Shet, M. N.; Ahmad, I.; Ajikumar, N.; Ramana, C. V. Unified Approach for the Total Synthesis of Bis-THF C15 Acetogenins: A Chloroenyne from *Laurencia majuscula*, Laurendecumenyne B and Laurefurenynes A/B. *Synthesis* 2021, *53* (16), 2903-2910. https://doi.org/10.1055/a-1500-1407

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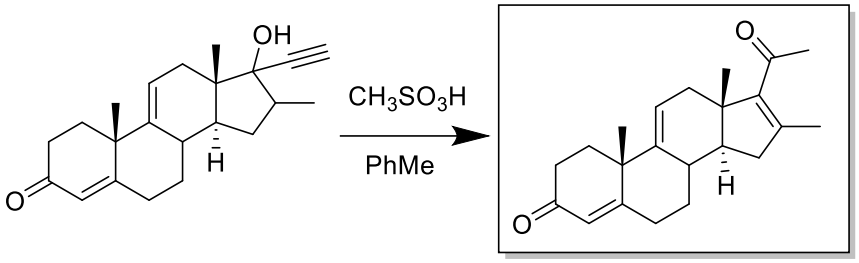

Wei, J.; Zhang, Y.; Liu, M.; Ning, Y.; Cao, Y.; Chen, F. Divergent Chemo- and Biocatalytic Route to 16 *β* -Methylcorticoids: Asymmetric Synthesis of Betamethasone Dipropionate, Clobetasol Propionate, and Beclomethasone Dipropionate. *Angew. Chem. Int. Ed.* 2024, *63* (4), e202313952. https://doi.org/10.1002/anie.202313952

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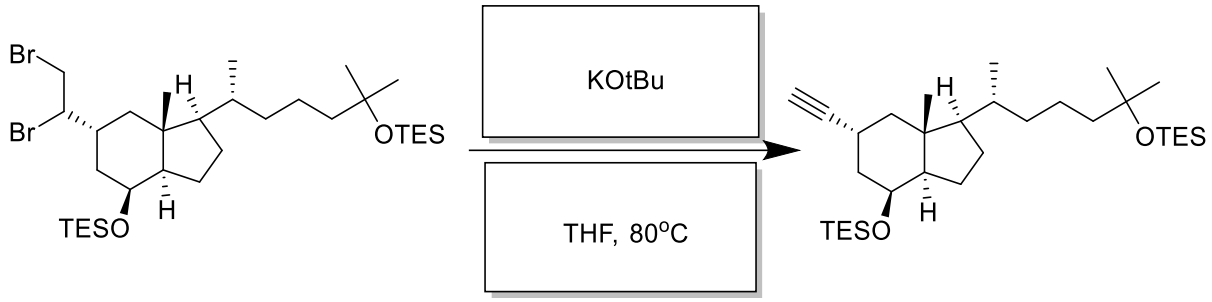

Iwaki, M.; Sakamoto, R.; Tsutsumi, R.; Sawada, T.; Hirokawa, T.; Kato, S.; Nagasawa, K. Development of an Environmentally Responsive Fluorescent Ligand for Vitamin D Receptor. *ChemBioChem* 2025, *26* (8), e202401038. https://doi.org/10.1002/cbic.202401038

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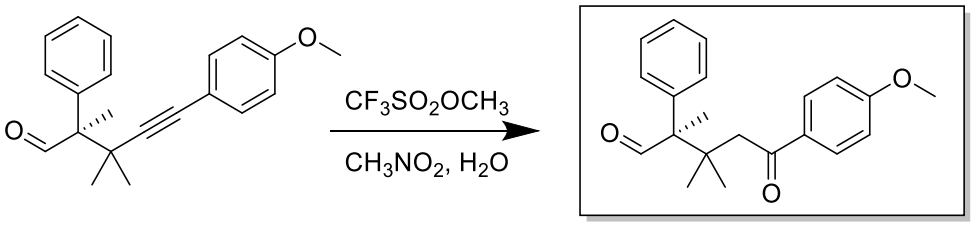
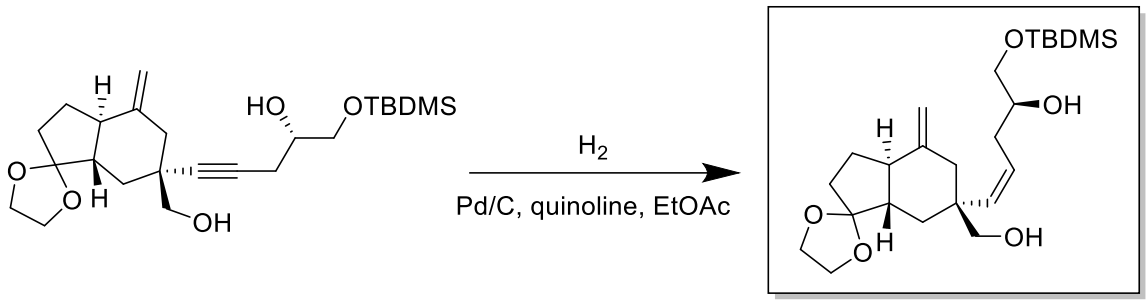


Note: Methyltriflate ($CF_3SO_2OCH_3$) reacts with water to form triflic acid (CF_3SO_2OH) and methanol.

Wu, S.; Xu, X.; Tang, T.; Deng, X.; Zhang, S.; Yan, C.-G.; Zhang, J.; Wang, M.; Wang, L. Enantioselective Synthesis of Quaternary Stereocenter Aldehydes by Palladium-Catalyzed Intermolecular Propargylation Reaction. *J. Am. Chem. Soc.* 2026, *148* (15), 16058–16067. https://doi.org/10.1021/jacs.6c00417

5.1.22



Zhang, Y.; Milkovits, A.; Agarawal, V.; Taylor, C. A.; Snyder, S. A. Total Synthesis of the Meroterpenoid Manginoid A as Fueled by a Challenging Pinacol Coupling and Bicycle-forming Etherification. *Angew. Chem. Int. Ed.* 2021, *60* (20), 11127–11132. https://doi.org/10.1002/anie.202016178

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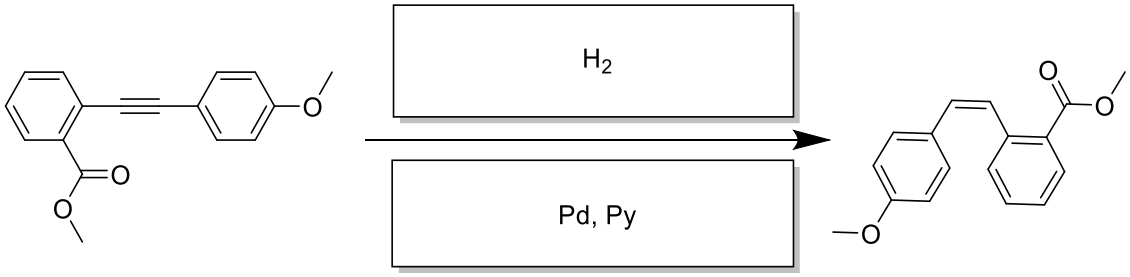
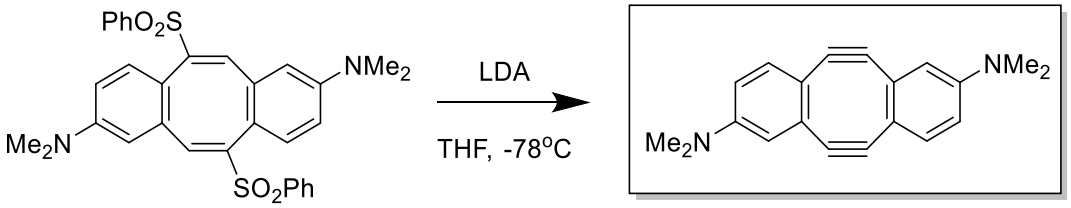


Pd, Py is a type of “poisoned catalyst”.

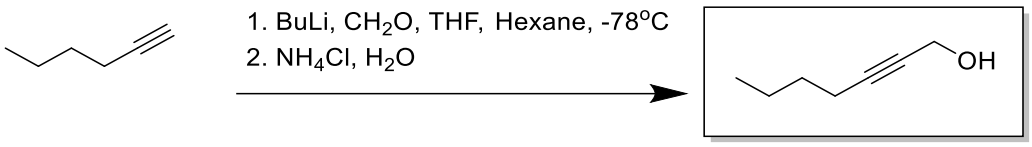
Sugano, M.; Fujiwara, T.; Mochizuki, W.; Inokuma, T.; Yamada, K. Catalyst-Controlled Regioselectivity Switching Inthe Bromolactonization of (*Z*)-StilbenecarboxylicAcids. *Org. Lett.* 2026, *28* (28), 8872–8877. https://doi.org/10.1021/acs.orglett.6c02195

5.1.24



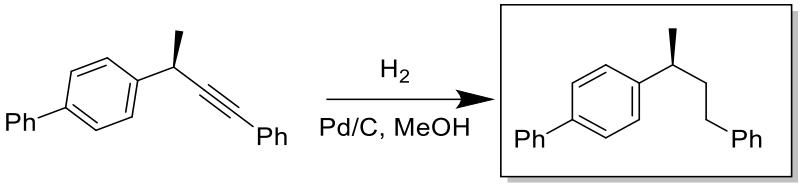
Sharma, K.; Strizhak, A. V.; Fowler, E.; Wang, X.; Xu, W.; Hatt Jensen, C.; Wu, Y.; Sore, H. F.; Lau, Y. H.; Hyvönen, M.; Itzhaki, L. S.; Spring, D. R. Water-Soluble, Stable and Azide-Reactive Strained Dialkynes for Biocompatible Double Strain-Promoted Click Chemistry. *Org. Biomol. Chem.* 2019, *17* (34), 8014-8018. https://10.1039/c9ob01745c

5.1.25



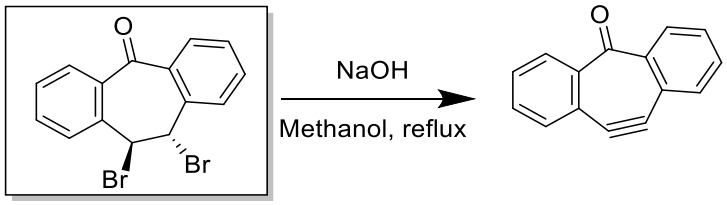
Ramesh, G.; Mishra, S.; Baire, B. A Hydrido-Alkynyl-Prins Cyclization Using Isopropanol as a Hydride Donor: Discovery, Scope and Mechanistic Study. *Org. Biomol. Chem.* 2026, *24* (25), 5355–5362. https://doi.org/10.1039/D6OB00688D

5.1.26



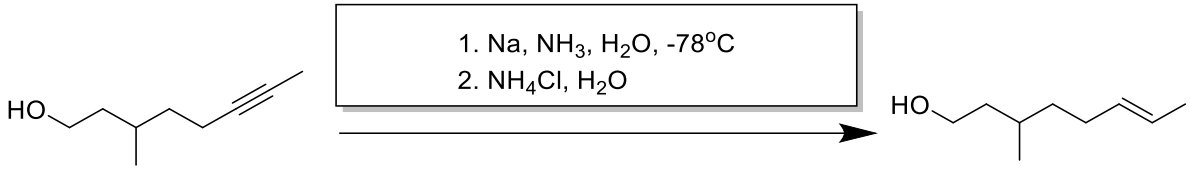
Gao, D.; Qin, L.-Z.; Li, Z.-L.; Gu, Q.-S.; Liu, X.-Y. Copper-Catalysed Enantioconvergent Radical C(Sp3)–C(Sp3) Cross-Coupling of Tertiary Electrophiles with Cyclopropanols for Quaternary Carbon Formation. *Nat. Synth.* 2026, *5* (5), 750–760. https://doi.org/10.1038/s44160-025-00987-1

5.1.27



Kornmayer, S.; Rominger, F.; Gleiter, R. Synthesis of 11,12-Didehydrodibenzo[a,e]Cycloocten-5(6H)-One: A Strained Eight-Membered Alkyne. *Synthesis* 2009, *2009* (15), 2547–2552. https://doi.org/10.1055/s-0029-1217404

5.1.28

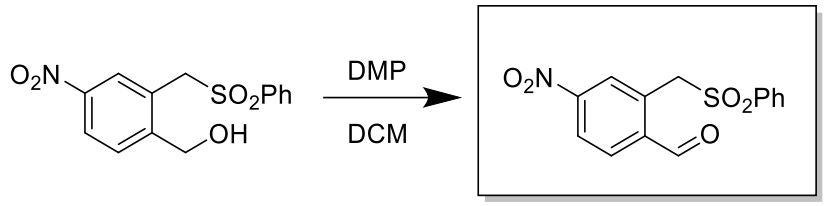


Vulovic, B.; Trmcic, M.; Matovic, R.; Saicic, R. N. Cyclization Reactions of Oxyallyl Cation. A Method for Cyclopentane Ring Formation. *Org. Lett.* 2019, *21* (23), 9618–9621. https://doi.org/10.1021/acs.orglett.9b03791

Section 6 – Box-Type Questions

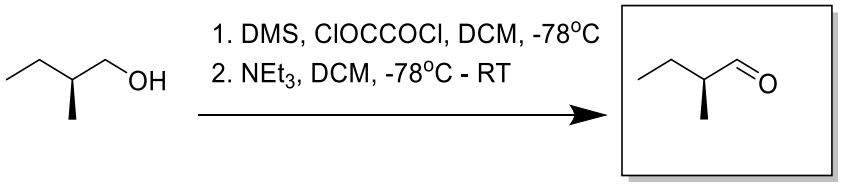
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

6.1.1



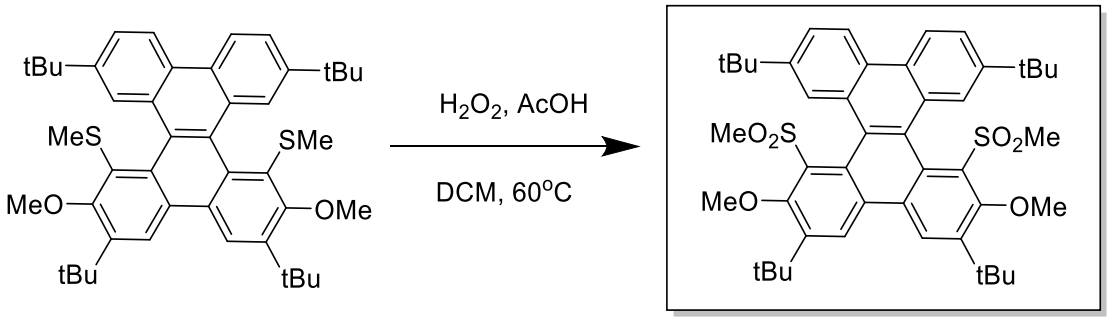
Sharma, K.; Strizhak, A. V.; Fowler, E.; Wang, X.; Xu, W.; Hatt Jensen, C.; Wu, Y.; Sore, H. F.; Lau, Y. H.; Hyvönen, M.; Itzhaki, L. S.; Spring, D. R. Water-Soluble, Stable and Azide-Reactive Strained Dialkynes for Biocompatible Double Strain-Promoted Click Chemistry. *Org. Biomol. Chem.* 2019, *17* (34), 8014-8018. https://10.1039/c9ob01745c

6.1.2



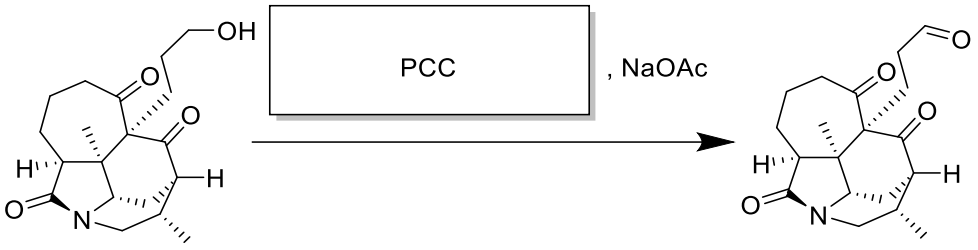
Rimle, L.; Pliatsika, D.; Arnold, N.; Kurth, S.; Kaiser, M.; Maser, P.; Kemmler, M.; Adams, M.; Riedl, R.; von Ballmoos, C. Dissecting Structural Requirements of Leucinostatin A Derivatives for Antiprotozoal Activity and Mammalian Toxicity. *J. Med. Chem.* 2025, *68* (4), 4237-4258. https://doi.org/10.1021/acs.jmedchem.4c01989.

6.1.3



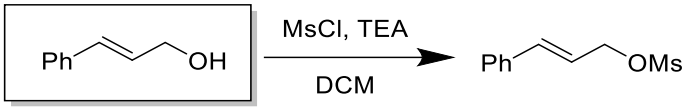
Yoshida, N.; Akasaka, R.; Yamaoka, Y.; Yashima, T.; Tokunaga, Y.; Iwasawa, T. Cross-Dimerization of Fluorenones for Synthesis of Dibenzo[g,p]chrysenes. *Tetrahedron* 2023, *143*, 133549. https://doi.org/10.1016/j.tet.2023.133549.

6.1.4



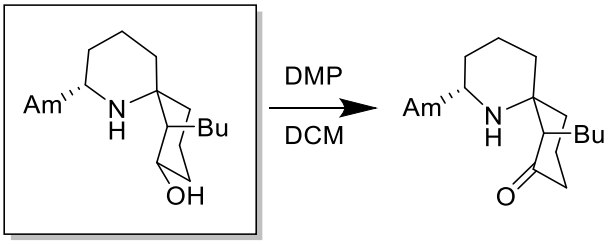
Zhang, Y.; Chen, Y.; Xu, J. Total Synthesis of Daphniphyllum Alkaloids: (+)-Daphlongamine E, (+)-Calyciphylline R, and (–)-10-Deoxydaphnipaxianine A. *Synthesis* 2024, *56* (08), 1273–1284. https://doi.org/10.1055/a-2244-1600

6.1.5



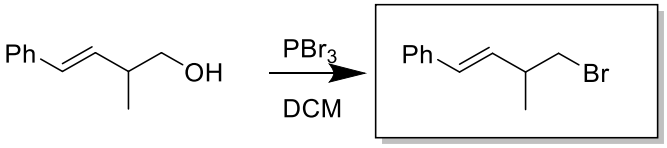
Li, J.; Yang, Y.; Cheng, L.; Xu, X.; Zhong, K.; Wang, T.; Chen, K.; Zhang, C.; He, C.; Xu, J.; Xu, S.; Luo, S. Discovery of 8-Quinolinesulfonamide Phenylimidazole-Based PKM2 Agonists for the Prevention and Delay of Aortic Dissection. *Eur. J. Med. Chem.* 2026, *304*, 118479. https://doi.org/10.1016/j.ejmech.2025.118479

6.1.6



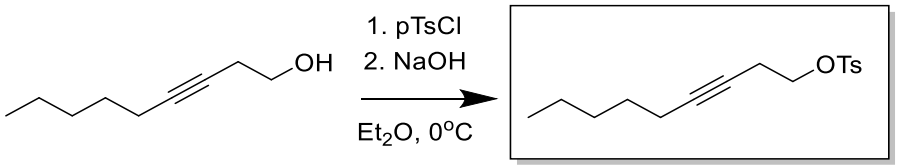
Nishikawa, K.; Ono, Y.; Mori, S.; Takayama, K.; Ihara, M.; Matsuda, K.; Morimoto, Y. Divergent Nine-Step Syntheses of Perhydrohistrionicotoxin Analogs and Their Inhibition Activity Toward Chicken α4β2-Neuronal Nicotinic Acetylcholine Receptors. *J. Org. Chem.* 2024, *89* (6), 4128–4133. https://doi.org/10.1021/acs.joc.3c02988

6.1.7



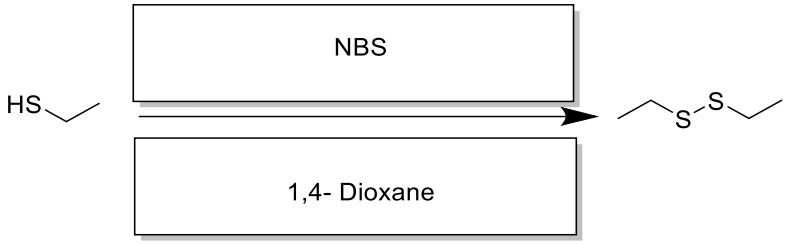
Tsai, S.; Huang, Y.; Chou, C. Carboxylate-Directed Palladium-Catalyzed Regioselective Mizoroki-Heck Alkenylation of γ , δ -Unsaturated Carboxylic Acids. *Adv. Synth. Catal.* 2023, *365* (5), 699–703. https://doi.org/10.1002/adsc.202201317

6.1.8



Ramesh, G.; Mishra, S.; Baire, B. A Hydrido-Alkynyl-Prins Cyclization Using Isopropanol as a Hydride Donor: Discovery, Scope and Mechanistic Study. *Org. Biomol. Chem.* 2026, *24* (25), 5355–5362. https://doi.org/10.1039/D6OB00688D

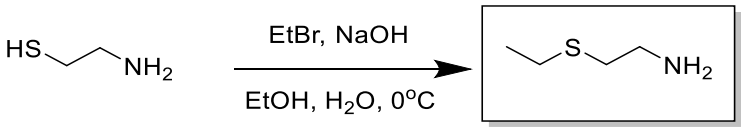
6.1.9



In introductory organic chemistry, common oxidants for thiols include air, bromine, and iodine in base. NBS can be viewed as a bromine equivalent and serves a similar oxidative function.

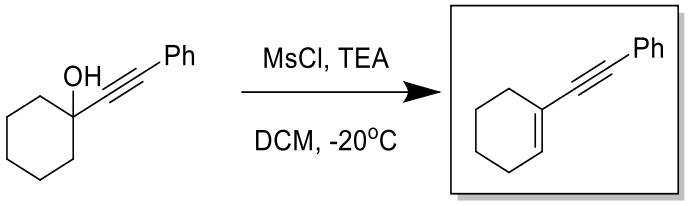
Yang, K.; Hu, Q.-Y.; Li, Q.; Liu, J.-X.; Li, Z.-Y.; Li, B.-J.; Sun, X.-Q. Metal-Free and NBS-Mediated Direct Thiol-Disulfide Exchange Reaction to Access Unsymmetrical Disulfides. *Eur. J. Org. Chem.* 2023, *26* (30), e202300394. https://doi.org/10.1002/ejoc.202300394

6.1.10



Wang, Z.; Lin, Q.; Ma, N.; Liu, S.; Han, M.; Yan, X.; Liu, Q.; Solan, G. A.; Sun, W.-H. Direct Synthesis of Ring-Fused Quinolines and Pyridines Catalyzed by NNHY-Ligated Manganese Complexes (Y = NR_2 or SR). *Catal. Sci. Technol.* 2021, *11* (24), 8026-8036. https://doi.org/10.1039/D1CY01945G

6.1.11



Belov, D. S.; Lukyanenko, E. R.; Kurkin, A. V.; Yurovskaya, M. A. Highly Stereoselective and Scalable Synthesis of *Trans* -Fused Octahydrocyclohepta[*b*]Pyrrol-4(1 *H*)-Ones via the Aza-Cope–Mannich Rearrangement in Racemic and Enantiopure Forms. *J. Org. Chem.* 2012, *77* (22), 10125–10134. https://doi.org/10.1021/jo301762a

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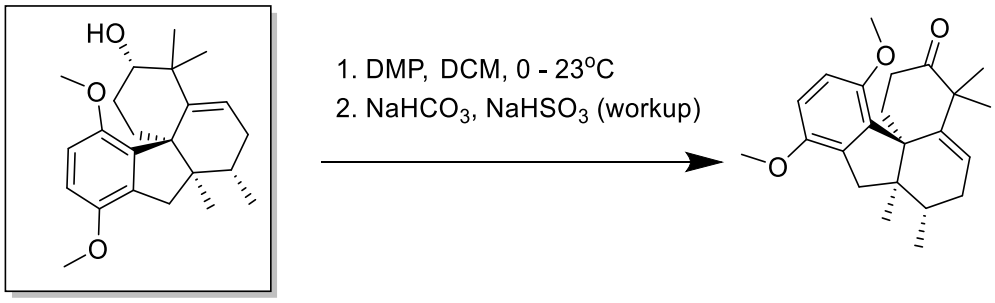
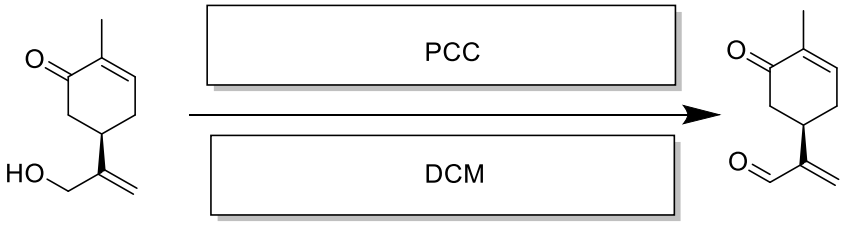


Chong, C.; Chang, L.; Grimm, I.; Zhang, Qunlong; Kuang, Y.; Wang, B.; Kang, J.; Liu, W.; Baars, J.; Guo, Y.; Schmalz, H.-G.; Lu, Z. Divergent Total Synthesis of the Revised Structures of Marine Anti-Cancer Meroterpenoids (+)-Dysiherbols A-E. *Chem. Sci.* 2023. *14* (12). 3302-3310. https://doi.org/10.1039/d3sc00173c

6.1.13



Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* 2024, *26* (22), 4648–4653. https://doi.org/10.1021/acs.orglett.4c01374

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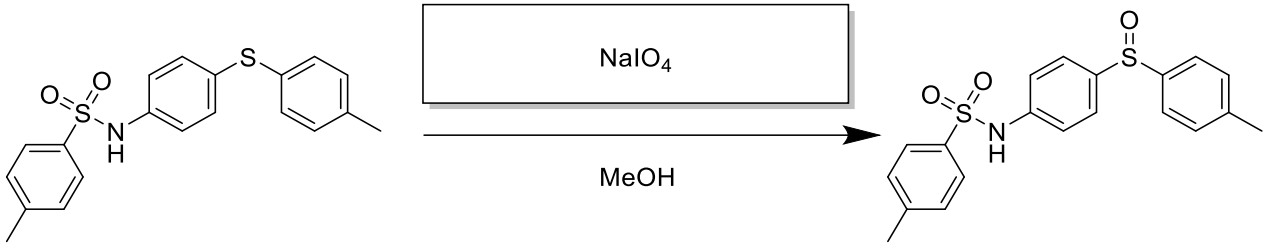

Bao, X.; Yao, J.; Zhou, H.; Xu, G. Nucleophilic Functionalizations of Aniline Derivatives: Aromatic Pummerer Reaction for Umpolung Halogenation and Hydroxylation on Benzene Ring. *Org. Lett.* 2017, *19* (21), 5780–5782. https://doi.org/10.1021/acs.orglett.7b02720

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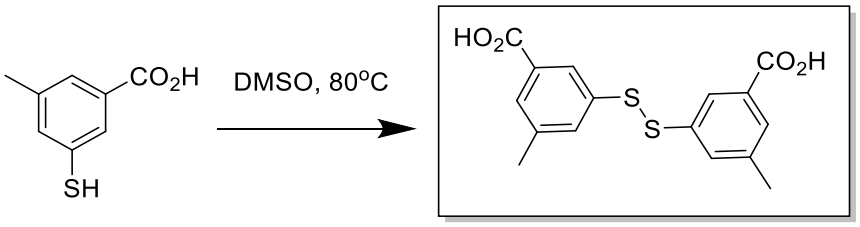

Xue, L.; Yu, J.; Zhou, K.; Zhong, Y.; Li, C.; Zhu, H.; Sun, H.; Yang, K.; Hu, Y. J. Metal-Free C–S Bond Formation: Enabling a Wide Array of Sulfides for DEL Synthesis. *Org. Lett.* 2025, *27* (21), 5412-5416. https://doi.org/10.1021/acs.orglett.5c01363

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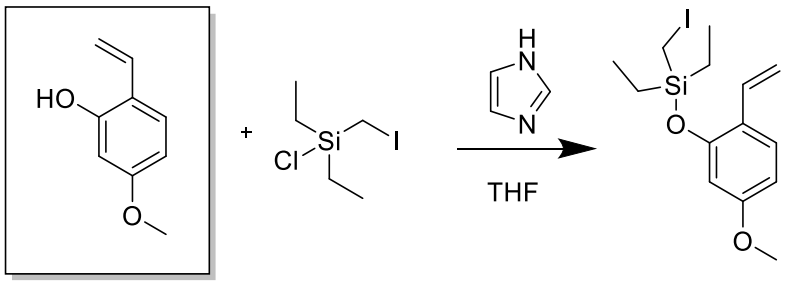
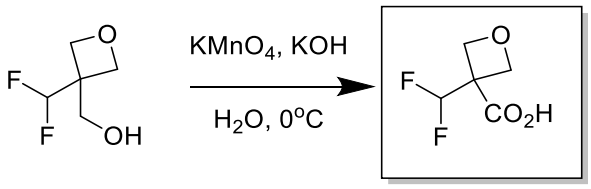


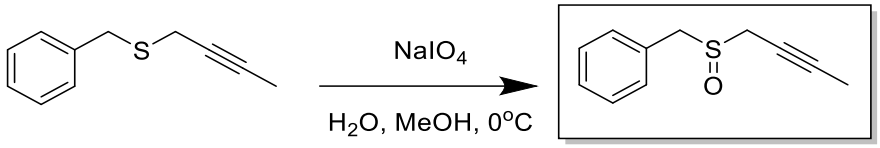
Parasram, M.; Laroshenko, V. O.; Gevorgyan, V. Endo-Selective Pd-Catalyzed Silyl Methyl Heck Reaction. *J. Am. Chem. Soc.* 2014, *136* (52), 17926-17929. https://doi.org/10.1021/ja5104525

6.1.17



Litskan, E. V.; Lynnyk, S. V.; Shypov, R. H.; Vashchenko, B. V.; Hoida, A. Ye.; Klymenko-Ulianov, O. O.; Gorlova, A. O.; Granat, D. S.; Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V. Fine-Tuning of Physicochemical Properties of 3,3-Disubstituted Oxetanes Introducing Fluorine Atom(s) on the Building Blocks Level. *Chem. Eur. J.* 2025, *31* (51), e202500940. https://doi.org/10.1002/chem.202500940

6.1.18



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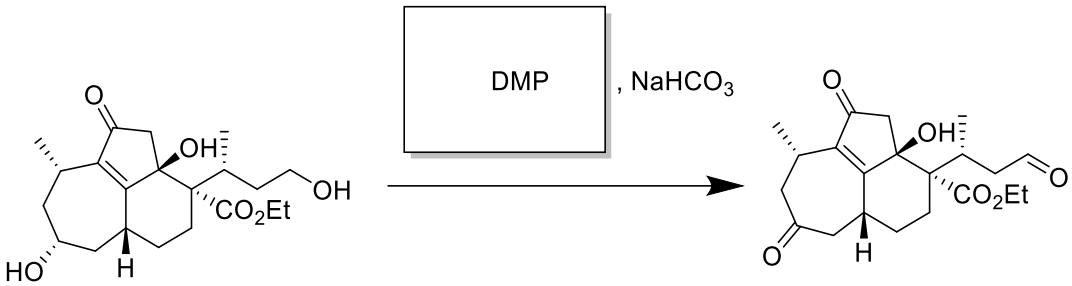

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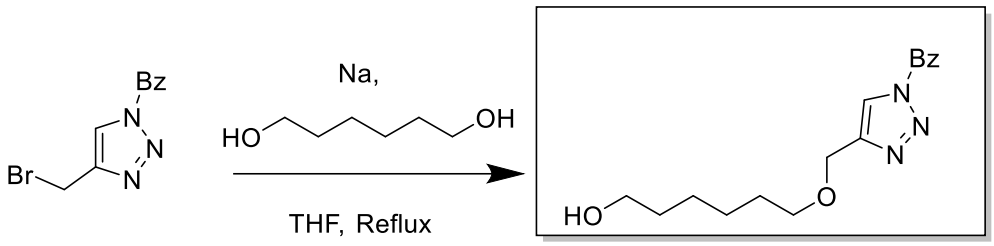

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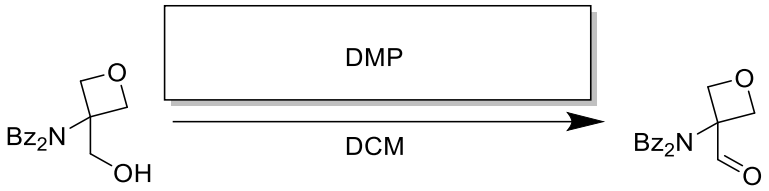

Litskan, E. V.; Lynnyk, S. V.; Shypov, R. H.; Vashchenko, B. V.; Hoida, A. Ye.; Klymenko-Ulianov, O. O.; Gorlova, A. O.; Granat, D. S.; Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V. Fine-Tuning of Physicochemical Properties of 3,3-Disubstituted Oxetanes Introducing Fluorine Atom(s) on the Building Blocks Level. *Chem. Eur. J.* 2025, *31* (51), e202500940. https://doi.org/10.1002/chem.202500940

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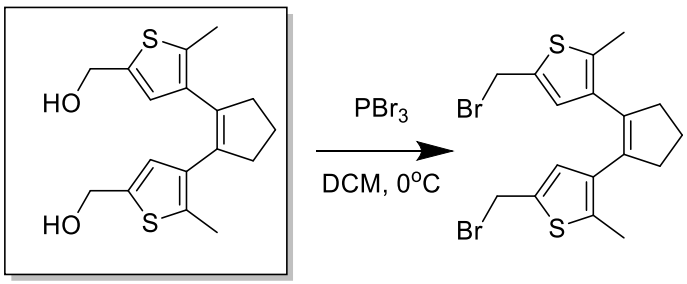

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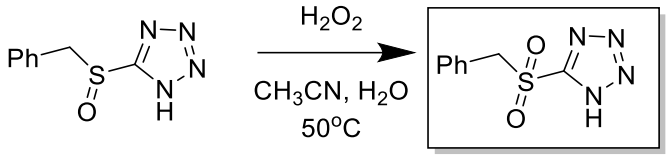

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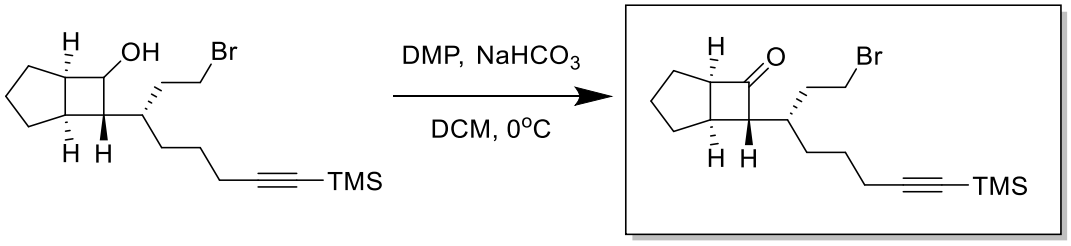

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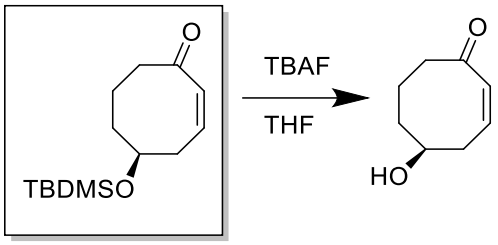

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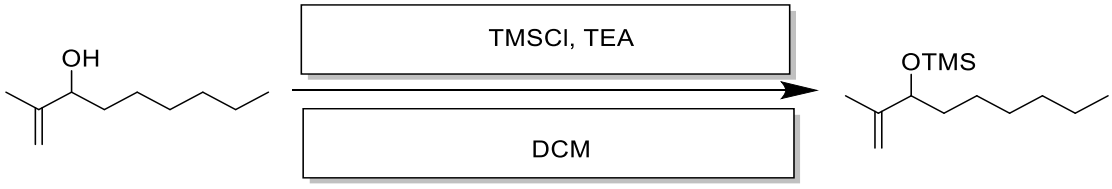

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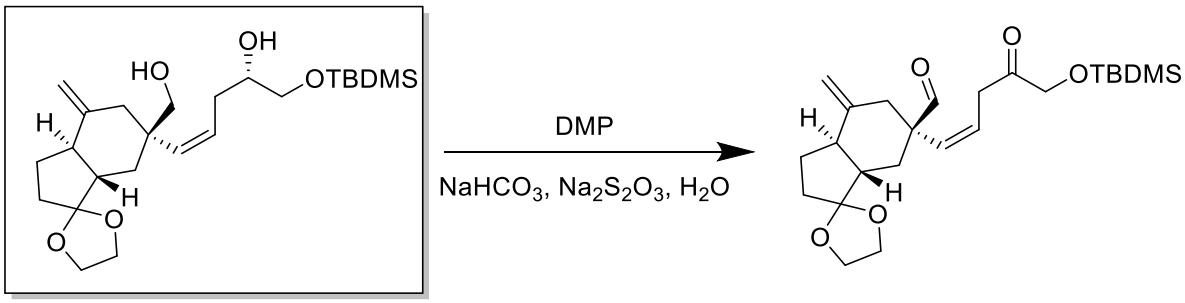

Zhang, Y.-A.; Milkovits, A.; Agarawal, V.; Taylor, C. A.; Snyder, S. A. Total Synthesis of the Meroterpenoid Manginoid A as Fueled by a Challenging Pinacol Coupling and Bicycle-Forming Etherification. *Angew. Chem. Int. Ed*. 2021, *60* (20), 11127–11132. https://doi.org/10.1002/anie.202016178

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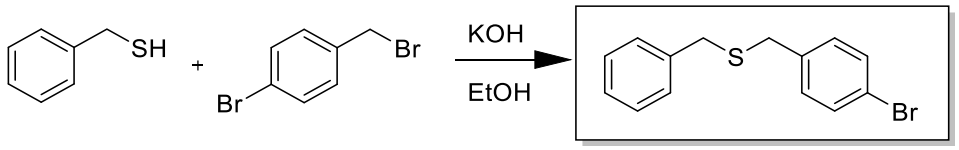

Tishchenko, E.; Lukina, V.; Niyazov, M.; Myznikov, L. 5-Alkylsulfonyl-1H-Tetrazoles: Oxidizers and Catalysts for the Oxidation of Sulfides to Sulfoxides with Hydrogen Peroxide. *Synthesis* 2026, *58* (06), 639–644. https://doi.org/10.1055/a-2759-9969

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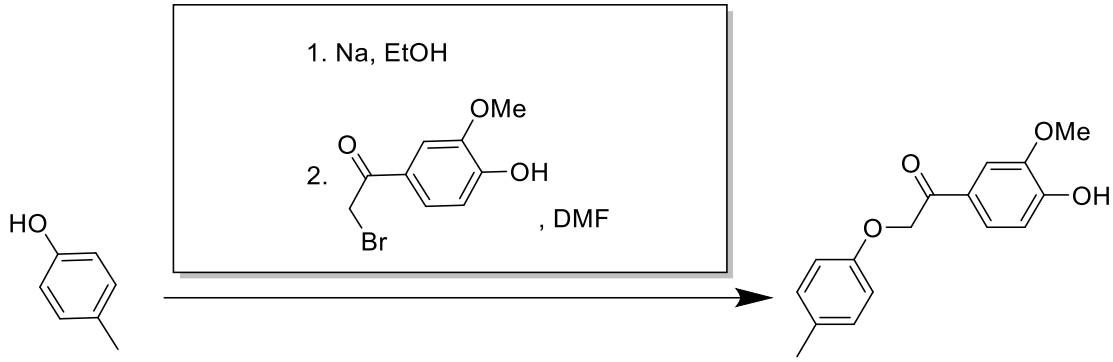

Nishimoto, T.; Nagamori, M.; Akai, N.; Nakaba, S.; Matsushita, Y. Incomplete Cleavage of β–O–4 Linkages Involving *p* -Hydroxyphenyl Units by Thioacidolysis and Elucidation of the Underlying Mechanism. *ACS Sustainable Chem. Eng.* 2026, *14* (14), 6914–6922. https://doi.org/10.1021/acssuschemeng.6c00262

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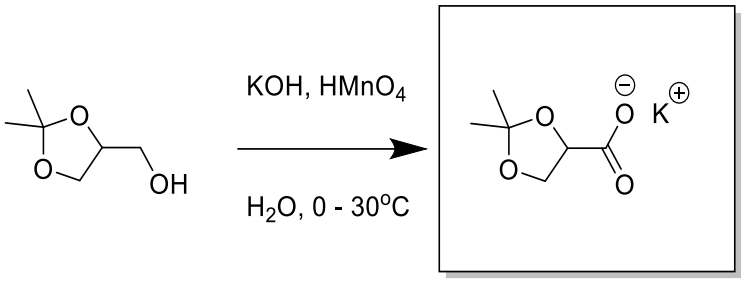

Chang, J. J.; Kumar, M.; Kashatus, R. C.; Tomaselli, D. J.; Kim, D. K. Substitutive Approach Toward Heteroaromatic Amino Alcohols Accessed Through Dioxolanyl Radical Linchpin. *Adv. Synth. Catal.* 2026, *368* (7), e70405. https://doi.org/10.1002/adsc.70405

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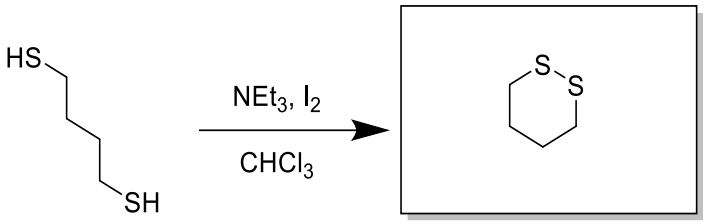

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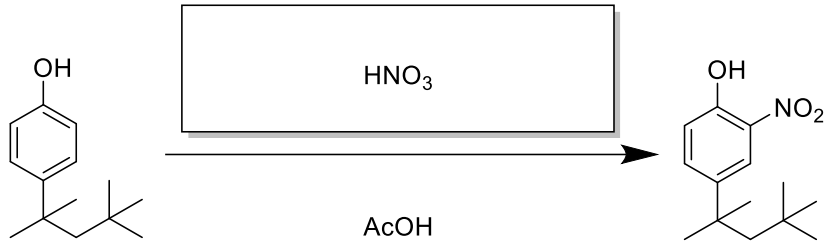
Section 7 – Box-Type Questions

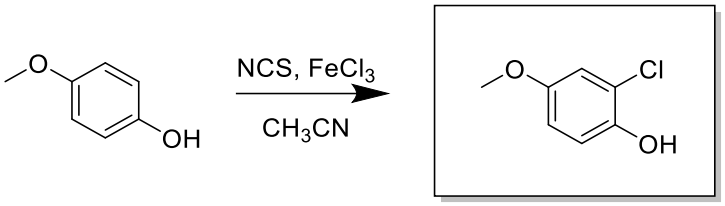
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

7.1.1



Wang, Y.-J.; Yang, X.-N.; Wang, F.; Wu, X.-F.; Shi, Y.-J.; Yang, Y.; Peng, X.-J.; Yi, H.; Li, K.; Yuan, J.; Li, Z.-R.; Gong, F.; Xue, S.-T. Design, Synthesis, and Antitumor Evaluation of Benzamide Derivatives Targeting HOXA1 Function. *J. Med. Chem.* **2026**, *69* (4), 4090-4111. https://doi.org/10.1021/acs.jmedchem.5c02745

7.1.2



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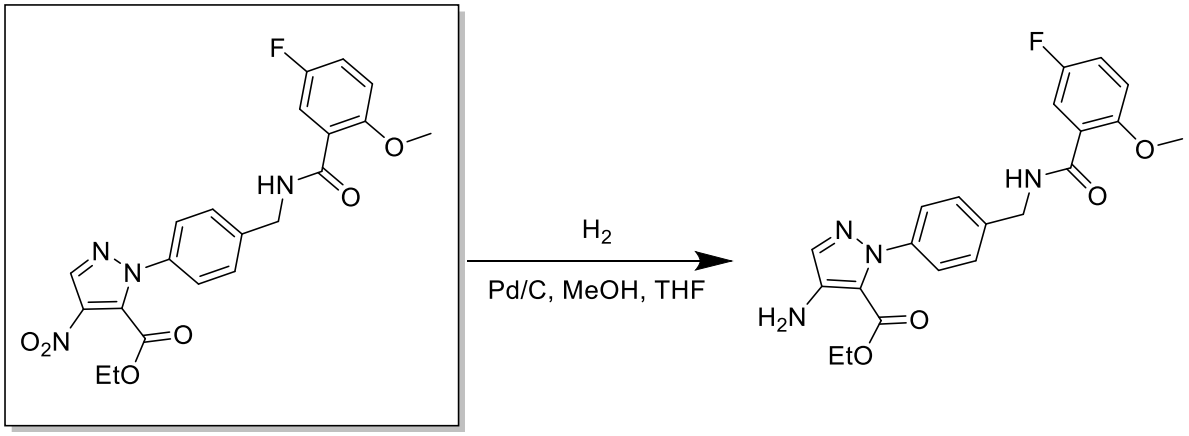

Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2026**, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

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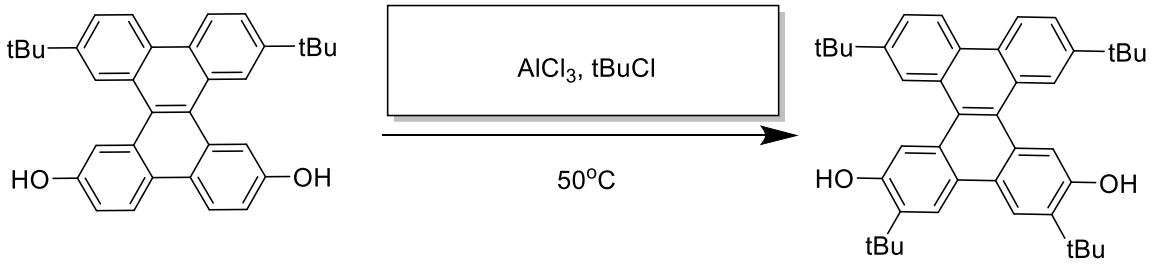

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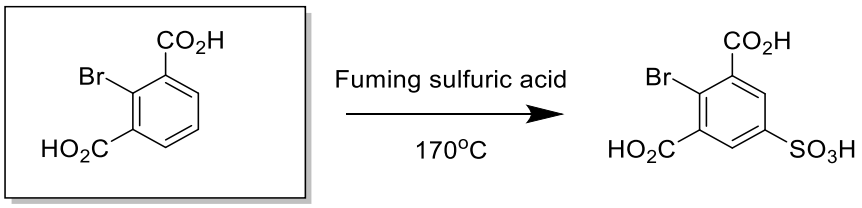

George, T. G.; Endeshaw, M. M.; Morgan, R. E.; Mahasenan, K. V.; Delfín, D. A.; Mukherjee, M. S.; Yakovich, A. J.; Fotie, J.; Li, C.; Werbovetz, K. A. Synthesis, Biological Evaluation, and Molecular Modeling of 3,5-Substituted-*N*1-Phenyl-*N*4,*N*4-di-*n*-butylsulfanilamides as Antikinetoplastid Antimicrotubule Agents. *Bioorg. Med. Chem.* **2007**, *15* (18), 6071-6079. https://doi.org/10.1016/j.bmc.2007.06.042

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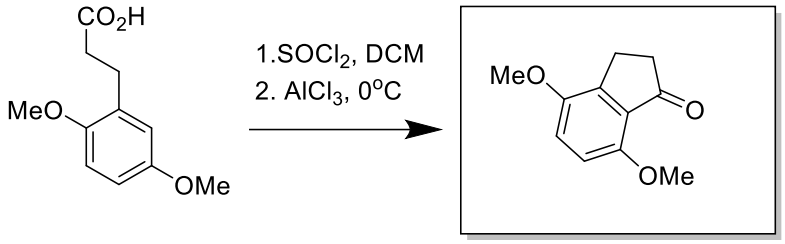

Note: $SOCl_2$ converts carboxylic acids into acid chlorides.

Gilbert, A.; Zuber, J.; Bach, T. Intramolecular *Ortho* Photocycloaddition of 4-Substituted 7-(4′-Alkenyloxy)-1-Indanones and Ensuing Reaction Cascades. *J. Org. Chem.* **2025**, *90* (11), 4099–4107. https://doi.org/10.1021/acs.joc.5c00171

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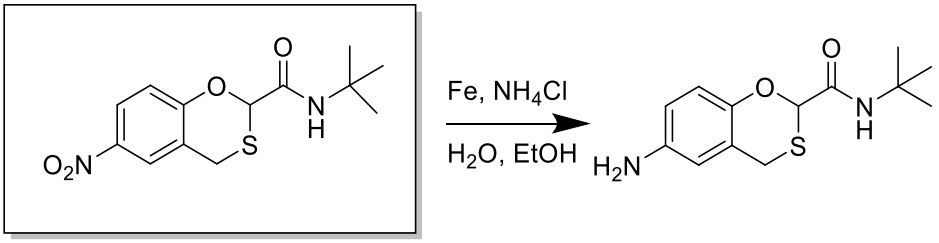

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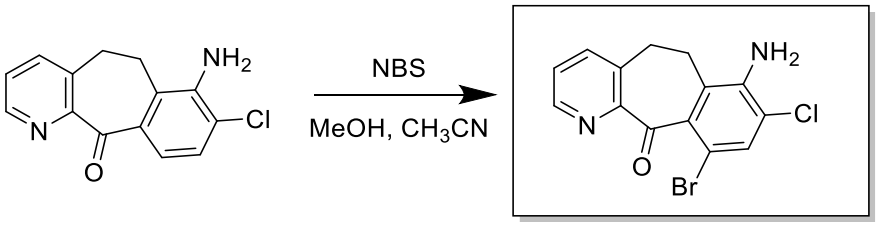

Fu, X.; McAllister, T. L.; Shi, X.; Thiruvengadam, T. K.; Tann, C.-H.; Lee, J. An Efficient One-Pot Process for 10-Bromo-8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one, an Intermediate to SCH 66336. *Org. Process Res. Dev.* **2003**, *7* (5), 692-695. https://doi.org/10.1021/op034054f

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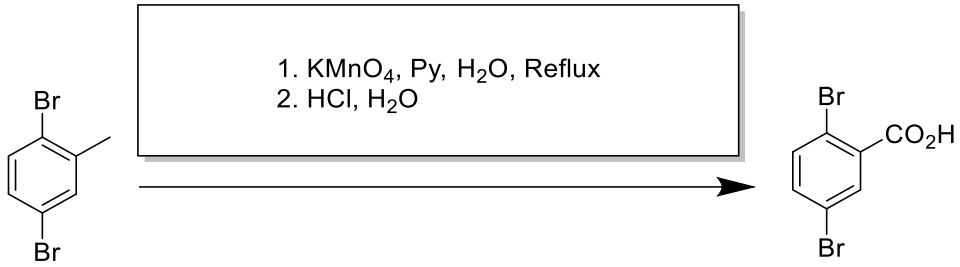

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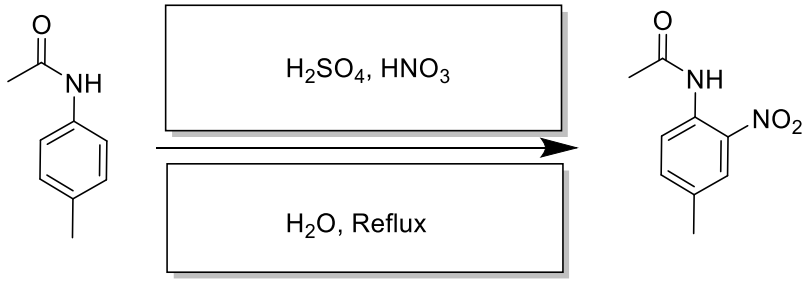

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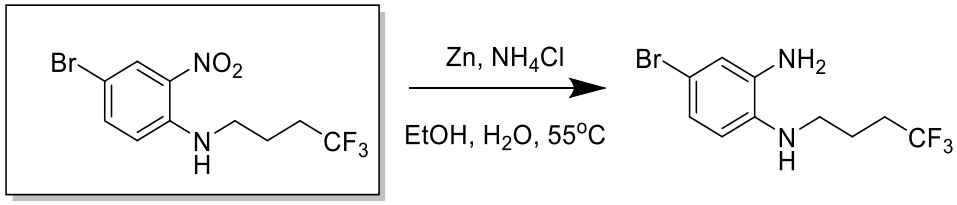

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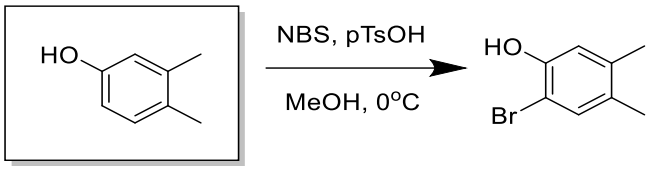

Stünkel, T.; Siebold, K.; Okumatsu, D.; Murata, K.; Ruyet, L.; Daniliuc, C. G.; Gilmour, R. *para*-Selective Dearomatization of Phenols by I(I)/I(III) Catalysis-Based Fluorination. *Chem. Sci.* **2023**, *14* (46), 13574-13580. https://doi.org/10.1039/D3SC05952A

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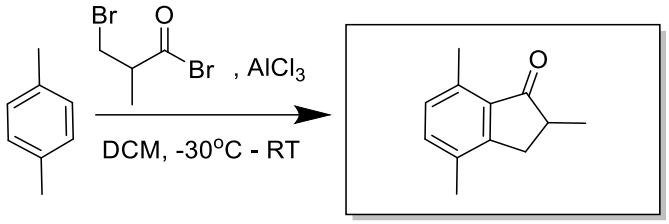

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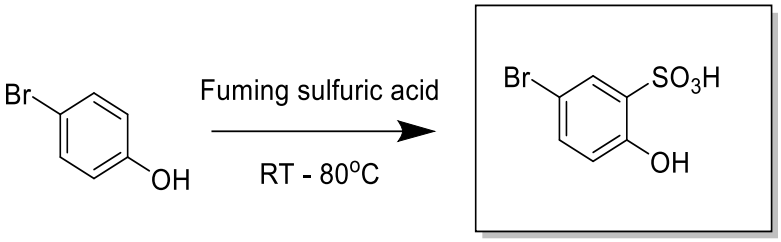

Deng, Z.-P.; Huo, L.-H.; Li, M.-S.; Zhang, L.-W.; Zhu, Z.-B.; Zhao, H.; Gao, S. Syntheses, Structures, and Luminescent Properties of Silver(I) Complexes Constructed from *ortho*-Hydroxyl Arenesulfonic Acids. *Cryst. Growth Des.* **2011**, *11* (7), 3090-3100. https://doi.org/10.1021/cg200360e

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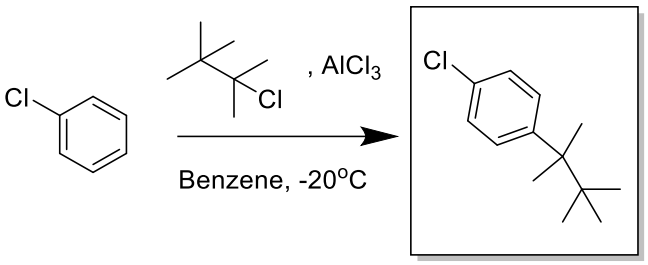

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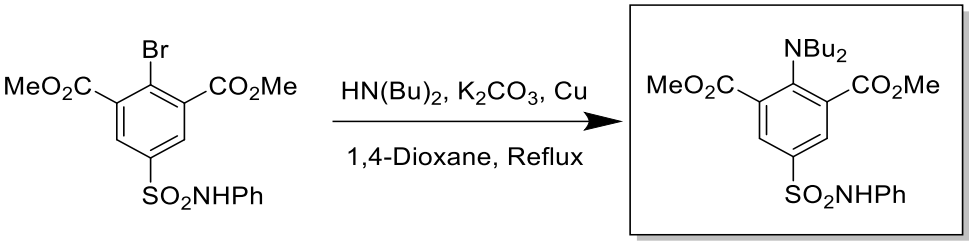
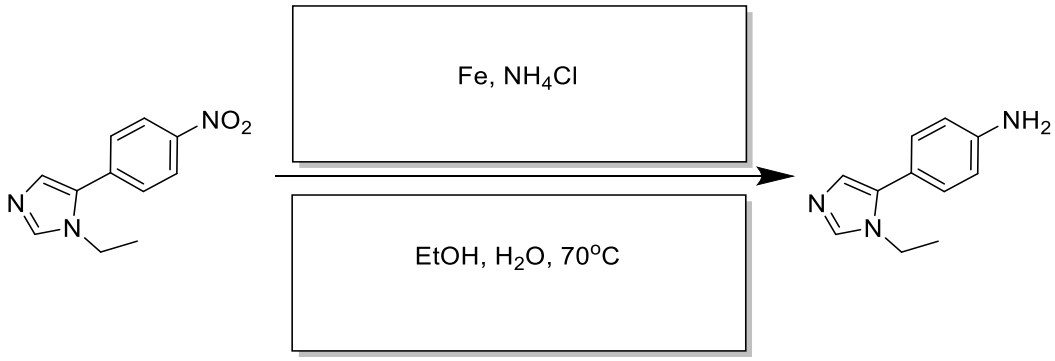


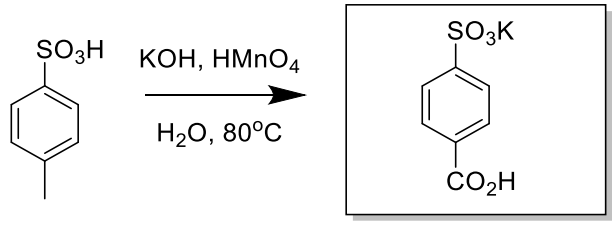
George, T. G.; Endeshaw, M. M.; Morgan, R. E.; Mahasenan, K. V.; Delfín, D. A.; Mukherjee, M. S.; Yakovich, A. J.; Fotie, J.; Li, C.; Werbovetz, K. A. Synthesis, Biological Evaluation, and Molecular Modeling of 3,5-Substituted-*N*1-Phenyl-*N*4,*N*4-di-*n*-butylsulfanilamides as Antikinetoplastid Antimicrotubule Agents. *Bioorg. Med. Chem.* **2007**, *15* (18), 6071-6079. https://doi.org/10.1016/j.bmc.2007.06.042

7.1.17



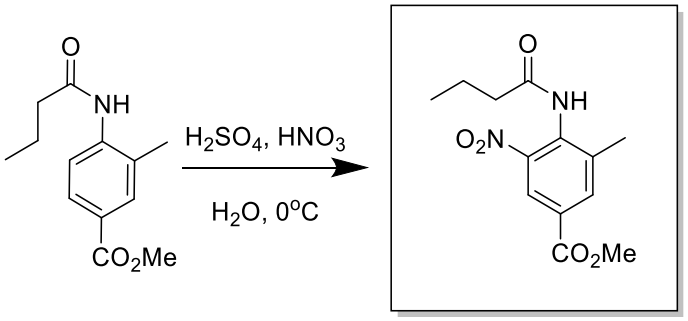
Li, J.; Yang, Y.; Cheng, L.; Xu, X.; Zhong, K.; Wang, T.; Chen, K.; Zhang, C.; He, C.; Xu, J.; Xu, S.; Luo, S. Discovery of 8-Quinolinesulfonamide Phenylimidazole-Based PKM2 Agonists for the Prevention and Delay of Aortic Dissection. *Eur. J. Med. Chem.* **2026**, *304*, 118479. https://doi.org/10.1016/j.ejmech.2025.118479

7.1.18



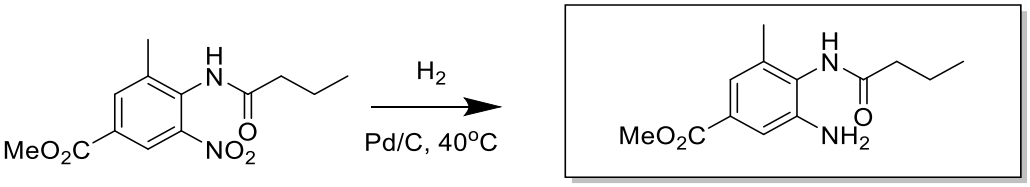
Huang, H.; Lu, W.; Li, X.; Cong, X.; Ma, H.; Liu, X.; Zhang, Y.; Che, P.; Ma, R.; Li, H.; Shen, X.; Jiang, H.; Huang, J.; Zhu, J. Design and Synthesis of Small Molecular Dual Inhibitor of Falcipain-2 and Dihydrofolate Reductase as Antimalarial Agent. *Bioorg. Med. Chem. Lett.* **2012**, *22* (2), 958-962. https://doi.org/10.1016/j.bmcl.2011.12.011

7.1.19



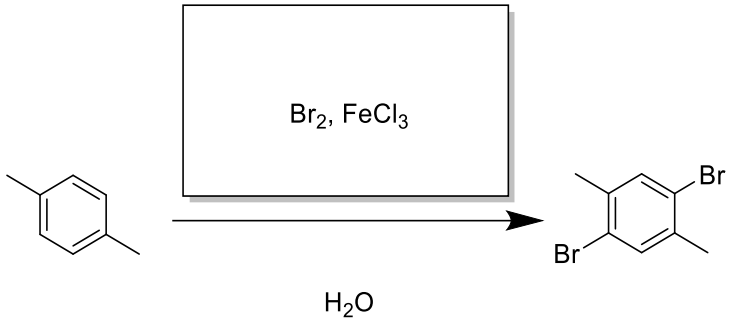
Zhang, Z.; Su, R.; Xiao, X.; Yang, J.; Zhang, G.; Wang, D.; Wang, S.; Wu, C. Efficient Synthesis of 1,7′-Dimethyl-2′-propyl-1H,3′H-2,5′-bibenzo[d]imidazole: Experiment, Crystal Structure, and DFT Calculations. *J. Mol. Struct.* **2026**, *1371*, 146521. https://doi.org/10.1016/j.molstruc.2026.146521

7.1.20



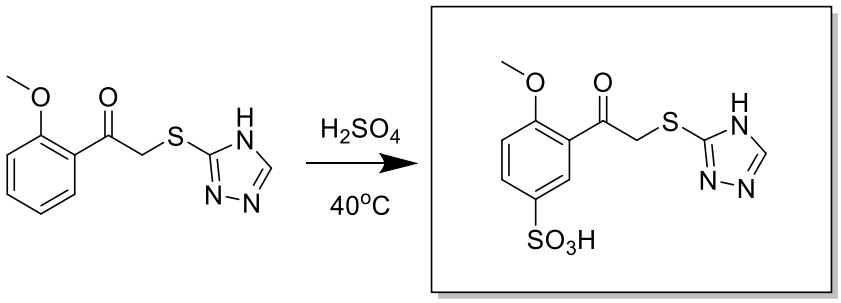
Zhang, Z.; Su, R.; Xiao, X.; Yang, J.; Zhang, G.; Wang, D.; Wang, S.; Wu, C. Efficient Synthesis of 1,7′-Dimethyl-2′-propyl-1H,3′H-2,5′-bibenzo[d]imidazole: Experiment, Crystal Structure, and DFT Calculations. *J. Mol. Struct.* **2026**, *1371*, 146521. https://doi.org/10.1016/j.molstruc.2026.146521

7.1.21



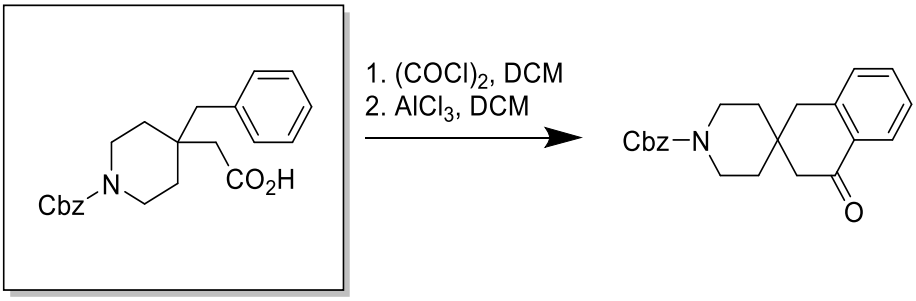
Fayoud, A.; Zorainy, M. Y. Selective Bromination of *p*-Xylene via Homogeneous Catalysis: Influence of Reaction Parameters on 2,5-Dibromo-*p*-Xylene Formation. *J. Phys.: Conf. Ser.* **2025**, *3051* (1), 012008. https://doi.org/10.1088/1742-6596/3051/1/012008

7.1.22



Krishnaraj, T.; Muthusubramanian, S. Synthesis of 6-Aryl-4*H*-imidazo[1,2-*b*][1,2,4]triazoles and 6-Aryl-thiazolo[3,2-*b*][1,2,4]triazoles. *J. Heterocycl. Chem.* **2015**, *52* (5), 1314-1320. https://doi.org/10.1002/jhet.2161

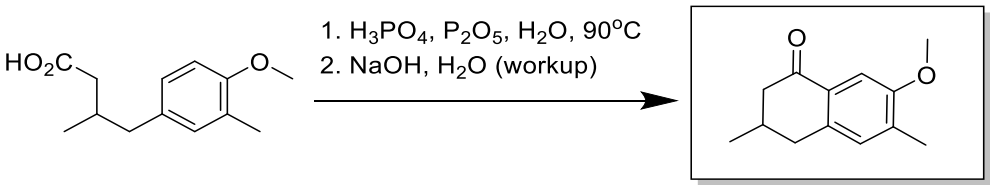
7.1.23



Note: $(COCl)_2$ is used to convert a carboxylic acid to an acid chloride.

Chu, G.-H.; Le Bourdonnec, B.; Gu, M.; Saeui, C. T.; Dolle, R. E. General and Efficient Synthetic Approach to Novel Tricyclic Spiroketones. *Tetrahedron* **2009**, *65* (27), 5161–5167. https://doi.org/10.1016/j.tet.2009.04.094

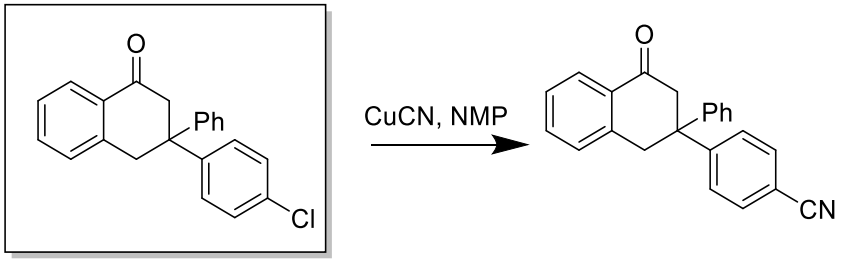
7.1.24



Hint: Step 1 is a strongly acidic condition.

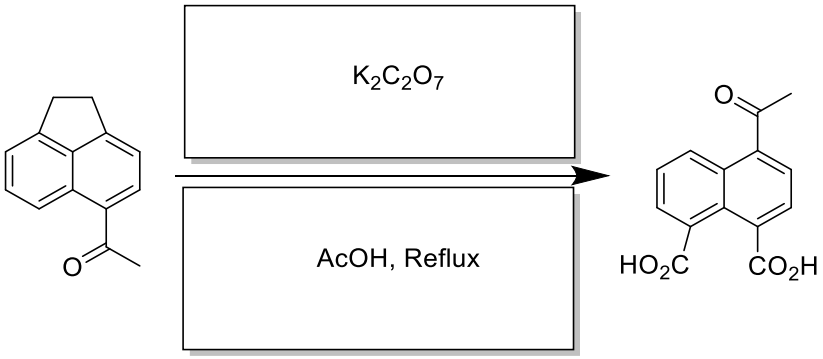
Roosen, P. C.; Karns, A. S.; Ellis, B. D.; Vanderwal, C. D. Evolution of a Short and Stereocontrolled Synthesis of (+)-7,20-Diisocyanoadociane. *J. Org. Chem.* **2022**, *87* (2), 1398–1420. https://doi.org/10.1021/acs.joc.1c02700

7.1.25



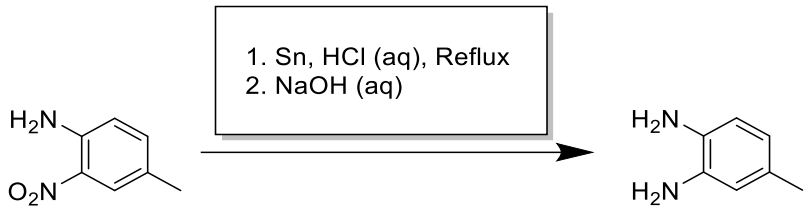
Zimmerman, H. E.; Suryanarayan, V. Organic Photochemical Rearrangements of Triplets and Zwitterions: Mechanistic and Exploratory Organic Photochemistry. *Eur. J. Org. Chem.* **2007**, *2007* (24), 4091-4102. https://doi.org/10.1002/ejoc.200700456

7.1.26



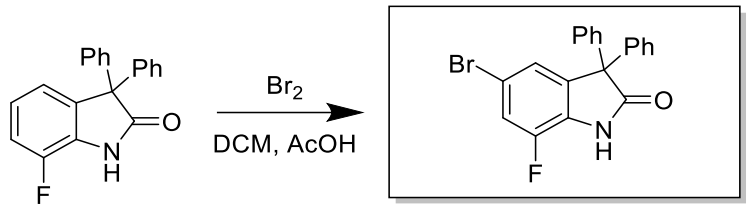
Dai, F.; Cao, Y.; Zhu, C.; Li, Y.; Ma, X.; Wang, S.; Liu, H.; Xie, X.; Gao, L.; Wang, Y.; Wang, C. Design, Synthesis, and Biological Evaluation of Naphthalimide-Polyamine Conjugate as a Potential Anti-Colorectal Cancer Agent. *Chem. Biodiversity* **2025**, *22* (4), e202401873. https://doi.org/10.1002/cbdv.202401873

7.1.27



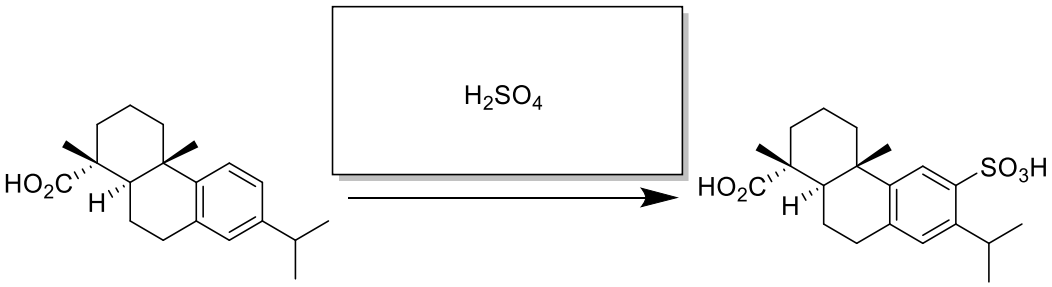
Glišić, B. Đ.; Hoffmann, M.; Warżajtis, B.; Genčić, M. S.; Blagojević, P. D.; Radulović, N. S.; Rychlewska, U.; Djuran, M. I. Selectivity of the Complexation Reactions of Four Regioisomeric Methylcamphorquinoxaline Ligands with Gold(III): X-Ray, NMR and DFT Investigations. *Polyhedron* **2016**, *105*, 137–149. https://doi.org/10.1016/j.poly.2015.12.009

7.1.28



Lamba, M.; Kumar, M.; Mane, M. V.; Goswami, A. Selectfluor-Mediated Directing Group and Transition Metal Catalyst-Free Site-Selective C7 Fluorination of 2-Oxindoles. *Adv. Synth. Catal.* **2026**, *368* (12), e70538. https://doi.org/10.1002/adsc.70538

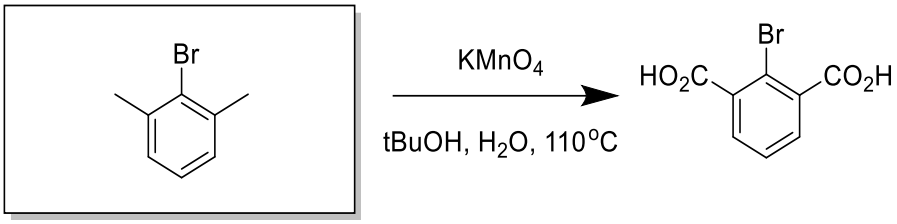
7.1.29



Note: The authors conducted this experiment at room temperature.

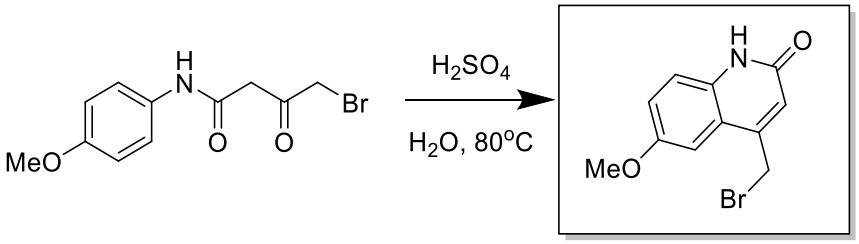
Huang, R.-Z.; Liang, G.-B.; Huang, X.-C.; Zhang, B.; Zhou, M.-M.; Liao, Z.-X.; Wang, H.-S. Discovery of Dehydroabietic Acid Sulfonamide Based Derivatives as Selective Matrix Metalloproteinases Inactivators That Inhibit Cell Migration and Proliferation. *Eur. J. Med. Chem.* **2017**, *138*, 979-992. https://doi.org/10.1016/j.ejmech.2017.07.020

7.1.30



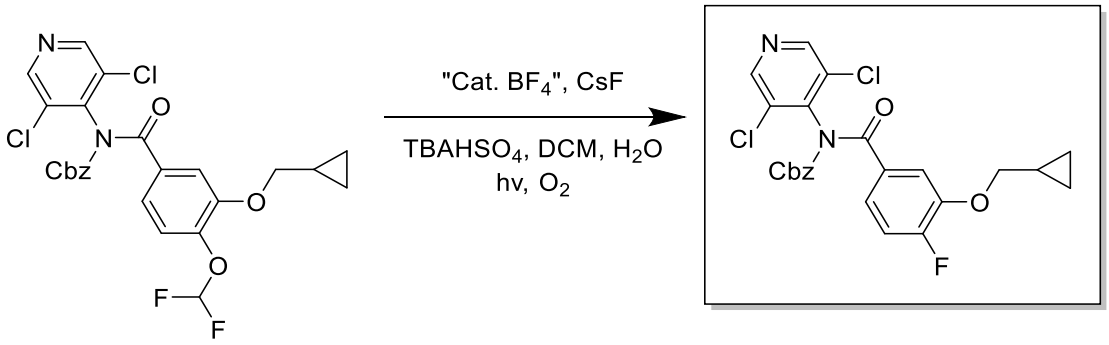
Narayanan, D.; Tran, K. T.; Pallesen, J. S.; Solbak, S. M. Ø.; Qin, Y.; Mukminova, E.; Luchini, M.; Vasilyeva, K. O.; González Chichón, D.; Goutsiou, G.; Poulsen, C.; Haapanen, N.; Popowicz, G. M.; Sattler, M.; Olagnier, D.; Gajhede, M.; Bach, A. Development of Noncovalent Small-Molecule Keap1-Nrf2 Inhibitors by Fragment-Based Drug Discovery. *J. Med. Chem.* **2022**, *65* (21), 14481–14526. https://doi.org/10.1021/acs.jmedchem.2c00830

7.1.31



Pan, G.; Qin, S.; Xu, D.; Kühn, F. E.; Guo, H. Visible Light-Induced Pericyclic Cascade Reaction for the Synthesis of Quinolinone Derivatives with an Oxabicyclo[4.2.0]octene Skeleton. *Org. Lett.* **2021**, *23* (8), 2959-2963. https://doi.org/10.1021/acs.orglett.1c00642

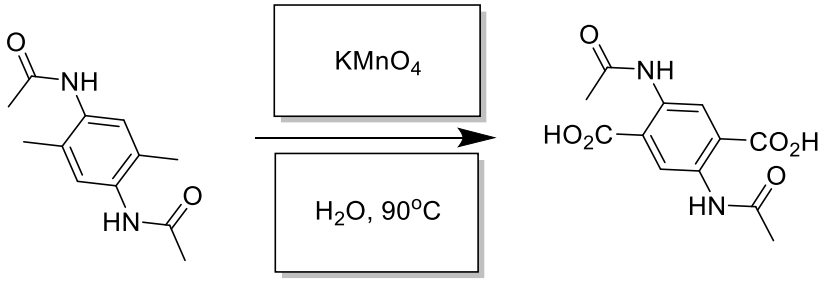
7.1.32



Note: For an introductory organic chemistry course, just focus on the CsF and the reactant.

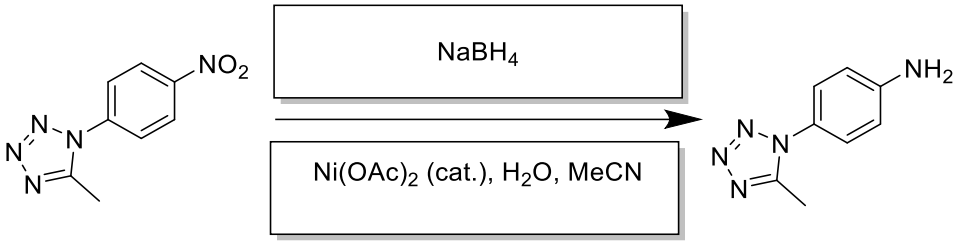
Mungalpara, M. N.; Wu, X.; Ma, X.; Zhu, Z.; Jiang, M.; Pike, V. W.; Lu, S.; Zhang, H.; Wu, Z.; Kinon, P. O.; Huang, Y.; Nicewicz, D. A.; Li, Z. Deoxyradiofluorination of Phenols via a Difluoromethoxy Nucleofuge Enabled by Organic Photoredox Catalysis. *ACS Cent. Sci.* **2026**, *12* (5), 638-648. https://doi.org/10.1021/acscentsci.6c00127

7.1.33



Bera, P.; Mukherjee, S.; Biswas, S. A Sustainable Pathway for CO2 Utilization: Pd(II)-Embedded Diamino-Functionalized Al(III) MOF Catalyst with High CO2 Sorption Affinity Enabling Recyclable Synthesis of Bioactive Quinazolinones under Atmospheric Pressure Conditions. *Inorg. Chem.* **2026**, *65* (33), 19495–19505. https://doi.org/10.1021/acs.inorgchem.6c02974

7.1.34



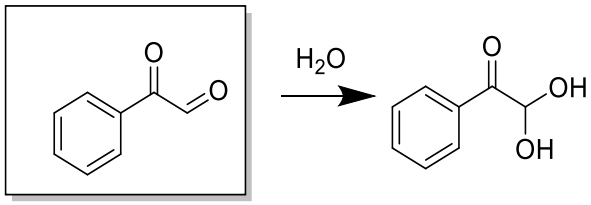
Learners in introductory organic chemistry typically learn to reduce the nitro group with tin or iron in acid or using catalytic hydrogenation and therefore may not propose what the authors used.

Sulakhe, S. M.; Khanzode, A. K.; Jamale, S. E.; Singh, M. B.; Singh, P.; Kumari, J.; Sriram, D.; Vedpathak, S. G.; Haval, K. P. New Benzofuran-Triazole-Tetrazole Conjugates: Synthesis, Antitubercular Evaluation, Molecular Docking, DFT, and MD Simulation. *J. Mol. Struct*. **2027**, *1379*, 147348. https://doi.org/10.1016/j.molstruc.2026.147348

Section 8a – Box-Type Questions

For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

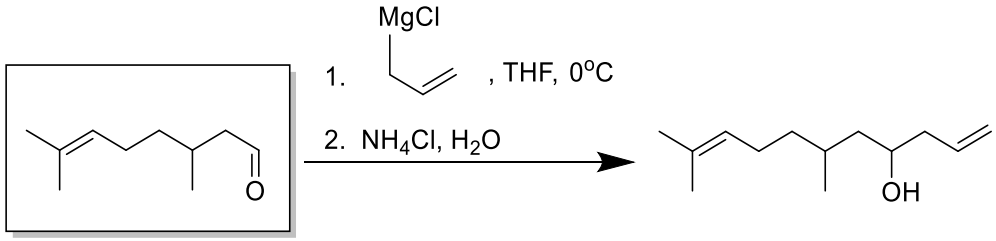
8a.1.1



Note: The authors did not need to add an acid catalyst for the reaction to work.

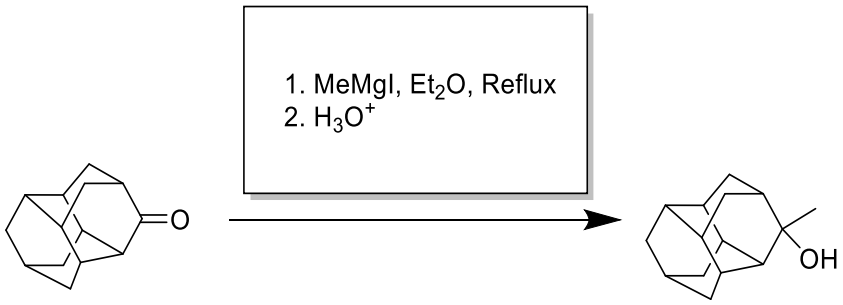
Wu, R.-H.; Du, Y.-D.; Tang, Y.-X.; Gou, Z.-Q.; Ye, W.; Zou, S.-P.; Xu, W.-H.; Wang, J.-G.; Wu, A.-X. A Genuine Four-Component Spirocyclization Reaction: Synthesis of Spiro[pyrimido[1,2-b]indazole] Ring Derivatives. *Adv. Synth. Catal.* **2026**, *368* (10), e70390. https://doi.org/10.1002/adsc.70390

8a.1.2



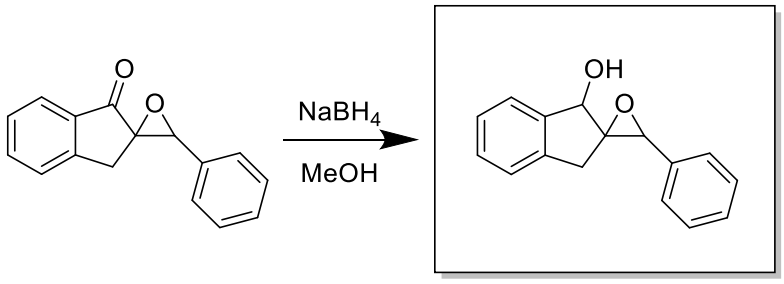
Zhang, Z.-K.; Lu, J.-A.; Zhang, S.; Zhang, J.-X.; Wang, D.-M.; Wu, Y.; Xu, Y.-Q.; Cao, Z.-Y.; Wang, P. Nickel-Catalyzed Remote Substitution of Alcohols. *J. Am. Chem. Soc.* **2026**, *148* (20), 20356–20363. https://doi.org/10.1021/jacs.6c07181.

8a.1.3



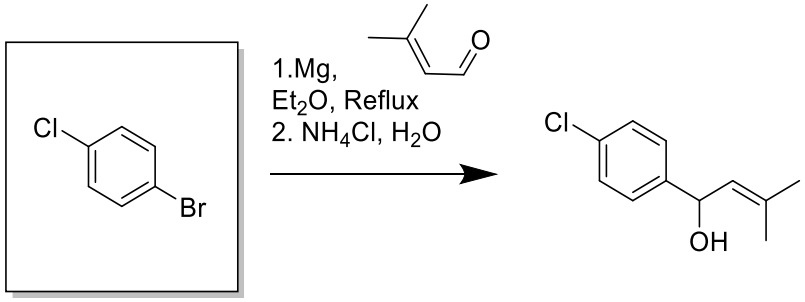
Fokin, A. A.; Zhuk, T. S.; Pashenko, A. E.; Dral, P. O.; Gunchenko, P. A.; Dahl, J. E. P.; Carlson, R. M. K.; Koso, T. V.; Serafin, M.; Schreiner, P. R. Oxygen-Doped Nanodiamonds: Synthesis and Functionalizations. *Org. Lett.* **2009**, *11* (14), 3068–3071. https://doi.org/10.1021/ol901089h

8a.1.4



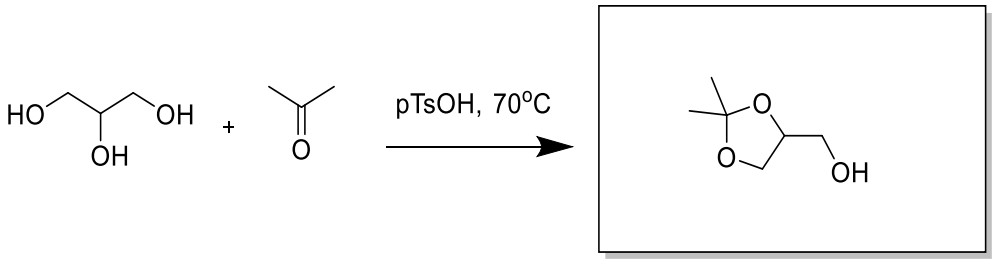
Qin, L.; Li, M.; Wang, X.; You, C.; Deng, G.; Chen, Y. Engineering of $P450_{PL2}$ Monooxygenase for the Stereoselective Synthesis of (*R*)-Styrene Oxides. *Org. Lett.* **2026**, *28* (8), 2567–2572. https://doi.org/10.1021/acs.orglett.5c05206

8a.1.5



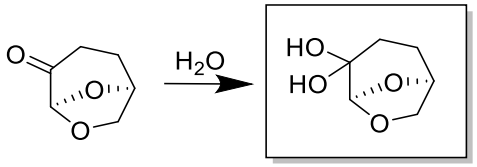
Tsai, S.; Huang, Y.; Chou, C. Carboxylate-Directed Palladium-Catalyzed Regioselective Mizoroki-Heck Alkenylation of *γ* , *δ* -Unsaturated Carboxylic Acids. *Adv. Synth. Catal.* **2023**, *365* (5), 699–703. https://doi.org/10.1002/adsc.202201317

8a.1.6



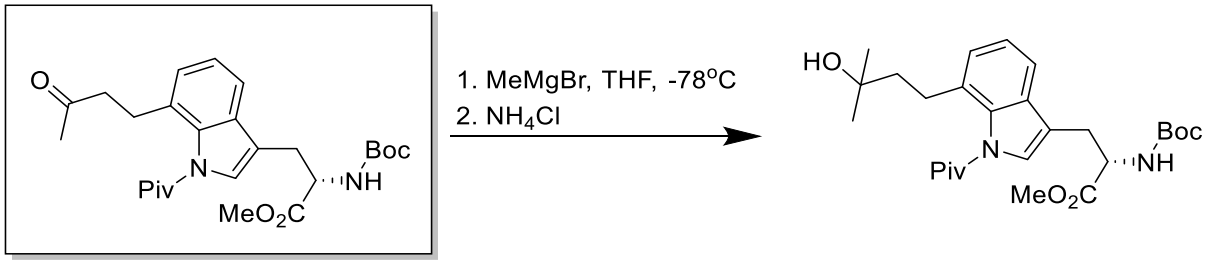
Chang, J. J.; Kumar, M.; Kashatus, R. C.; Tomaselli, D. J.; Kim, D. K. Substitutive Approach Toward Heteroaromatic Amino Alcohols Accessed Through Dioxolanyl Radical Linchpin. *Adv. Synth. Catal.* **2026**, *368* (7), e70405. https://doi.org/10.1002/adsc.70405

8a.1.7



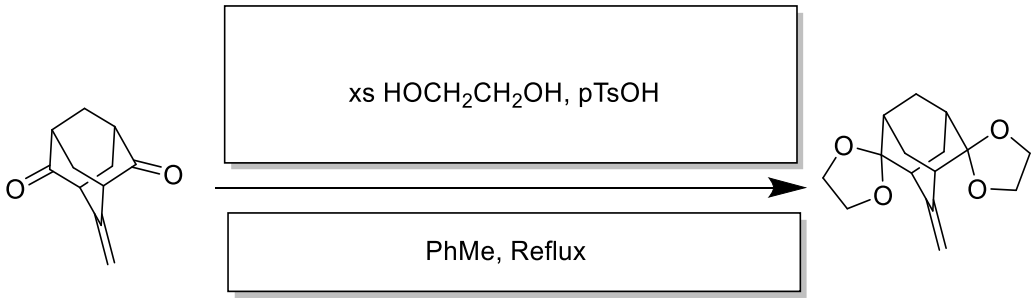
Dejaegere, A.; Napoli, A.; Heugebaert, T. S. A.; Stevens, C. V. Continuous Dihydrolevoglucosenone Recovery Using Commercial Membrane Technology. *Org. Process Res. Dev.* **2025**, *29* (4), 1076–1082. https://doi.org/10.1021/acs.oprd.4c00494

8a.1.8



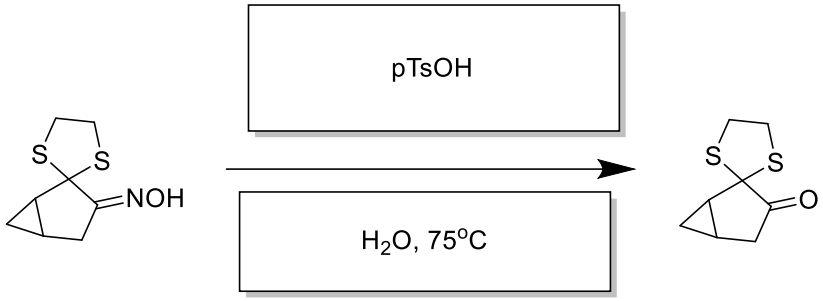
Devarajappa, R.; Hanessian, S. Total Synthesis of Asperdinones B, C, D, E and Terezine D. *Beilstein J. Org. Chem.* **2025**, *21*, 2730–2738. https://doi.org/10.3762/bjoc.21.210

8a.1.9



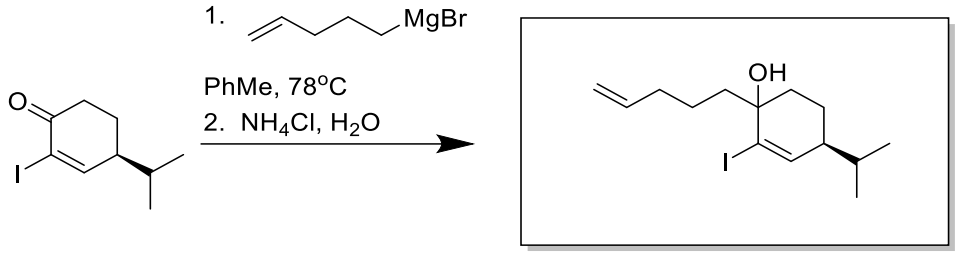
Ling, Y.; Zhang, P.; Sun, L.; Lai, W.; Luo, J. Efficient Synthesis of 2,2,4,4,6,6-Hexanitroadamantane under Mild Conditions. *Synthesis* **2014**, *46* (16), 2225–2233. https://doi.org/10.1055/s-0033-1341251

8a.1.10



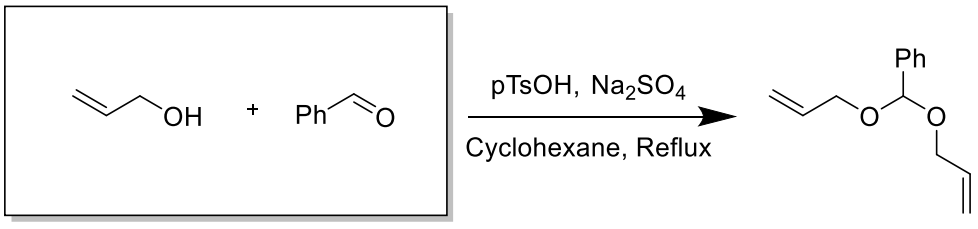
Kadunce, N.; St-Jean, O.; Cagulada, A.; Chang, W.-T. T.; Goldberg, A. F. G.; Huang, Z.; Kang, J.; Kim, J.; Kwon, K.; Lapina, O.; Lin, L.; Rainey, T. J.; Roever, L.; Shah, N. P.; Wolckenhauer, S. A. Synthetic Development and Scale-Up of a Complex Pyrazole Fragment of Lenacapavir. *Org. Process Res. Dev.* **2024**, *28* (8), 3368-3381. https://doi.org/10.1021/acs.oprd.4c00235

8a.1.11



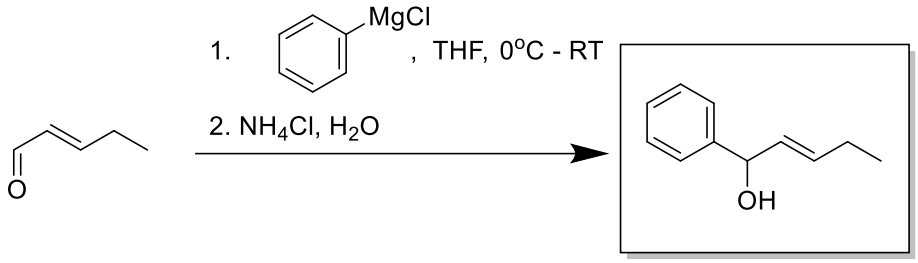
Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* **2009**, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

8a.1.12



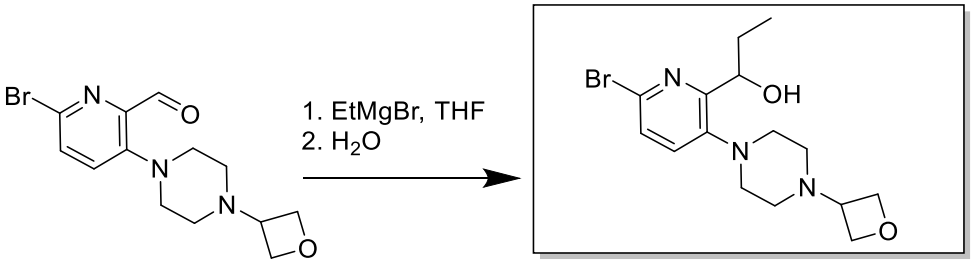
Ghosh, A. K.; Belcher, M. R. Lewis Acid-Catalyzed Vinyl Acetal Rearrangement of 4,5-Dihydro-1,3-Dioxepines: Stereoselective Synthesis of *Cis*- and *Trans*- 2,3-Disubstituted Tetrahydrofurans. *J. Org. Chem.* **2020**, *85* (16), 10399–10412. https://doi.org/10.1021/acs.joc.0c00390

8a.1.13



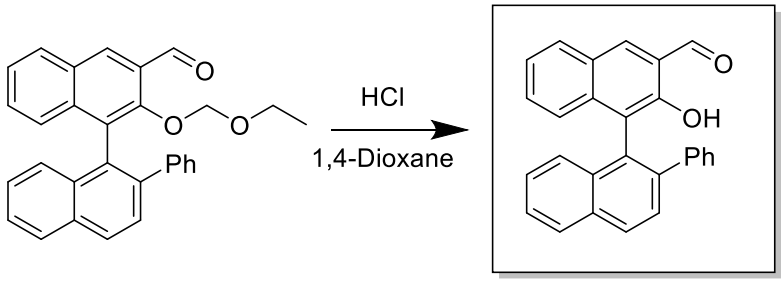
Yang, X.; Zhao, D.; Liu, Y.; Zhu, C. Palladium-Catalyzed Migratory Allylic Sulfonylation of Allylic Alcohols Using Sulfonyl Hydrazides. *Org. Biomol. Chem.* **2026**, *24* (24), 5057–5063. https://doi.org/10.1039/D6OB00512H

8a.1.14



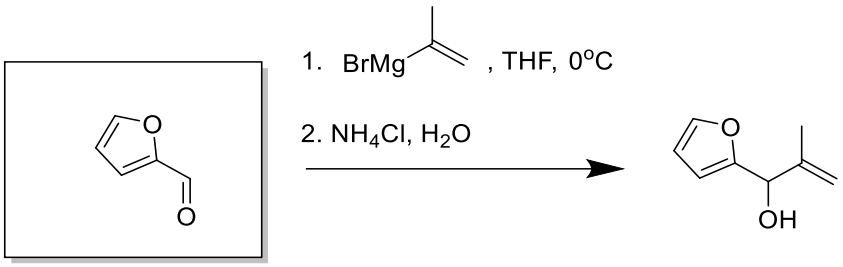
Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2026**, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

8a.1.15



Sandvoß, A.; Maag, H.; Daniliuc, C. G.; Schollmeyer, D.; Wahl, J. M. Dynamic Kinetic Resolution of Transient Hemiketals: A Strategy for the Desymmetrisation of Prochiral Oxetanols. *Chem. Sci.* **2022**, *13* (21), 6297–6302. https://doi.org/10.1039/D2SC01547A

8a.1.16



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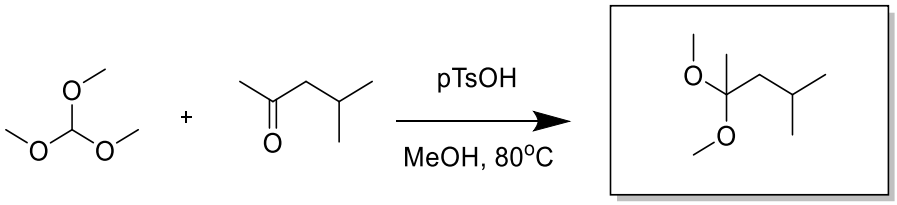
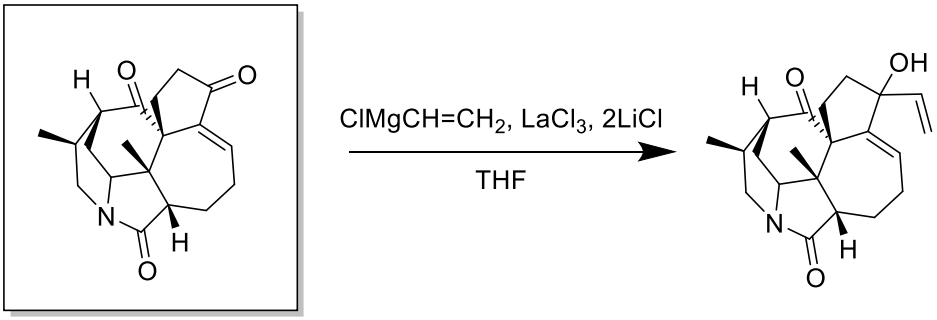
8a.1.17



Wang, R.-H.; Li, J.-F.; Li, Y.; Qi, S.-L.; Zhang, T.; Luan, Y.-X.; Ye, M. Selective C(Sp^3)–H Cleavage of Enamides for Synthesis of 2-Pyridones via Ligand-Enabled Ni–Al Bimetallic Catalysis. *ACS Catal.* **2021**, *11* (2), 858–864. https://doi.org/10.1021/acscatal.0c04585

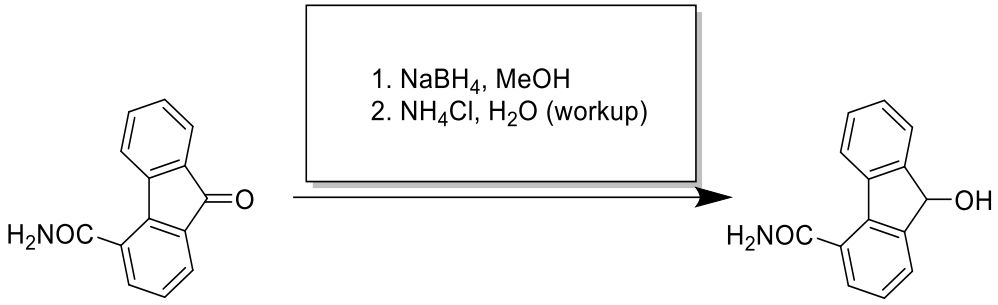
8a.1.18



Note: For an introductory organic chemistry course, you do not need to know how $LaCl_3$ and LiCl participate in the reaction.

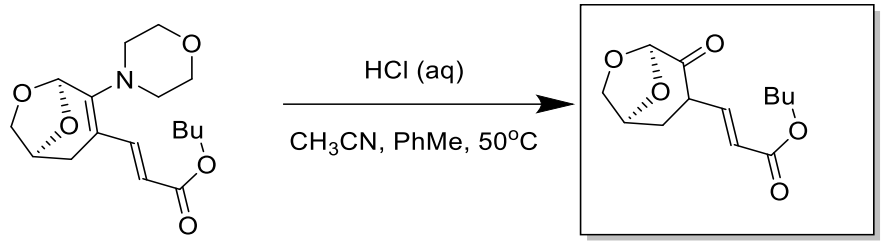
Zhang, Y.; Chen, Y.; Xu, J. Total Synthesis of Daphniphyllum Alkaloids: (+)-Daphlongamine E, (+)-Calyciphylline R, and (–)-10-Deoxydaphnipaxianine A. *Synthesis* **2024**, *56* (08), 1273–1284. https://doi.org/10.1055/a-2244-1600

8a.1.19



Narayanan, D.; Tran, K. T.; Pallesen, J. S.; Solbak, S. M. Ø.; Qin, Y.; Mukminova, E.; Luchini, M.; Vasilyeva, K. O.; González Chichón, D.; Goutsiou, G.; Poulsen, C.; Haapanen, N.; Popowicz, G. M.; Sattler, M.; Olagnier, D.; Gajhede, M.; Bach, A. Development of Noncovalent Small-Molecule Keap1-Nrf2 Inhibitors by Fragment-Based Drug Discovery. *J. Med. Chem.* **2022**, *65* (21), 14481–14526. https://doi.org/10.1021/acs.jmedchem.2c00830

8a.1.20



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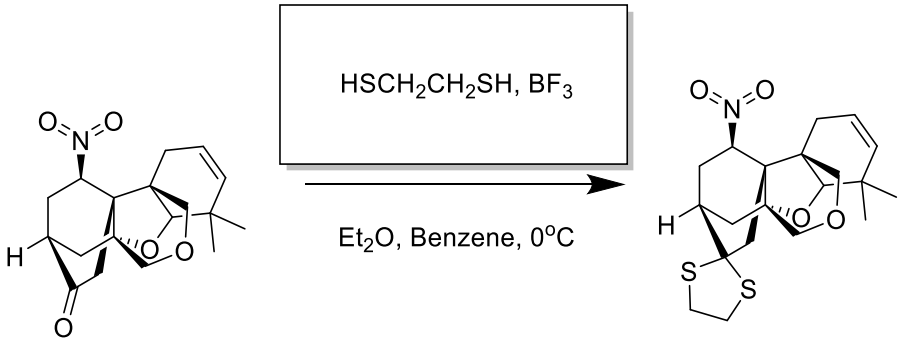
8a.1.21



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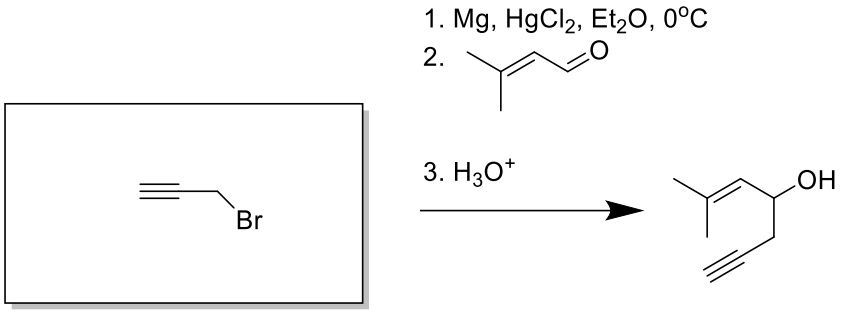
8a.1.22



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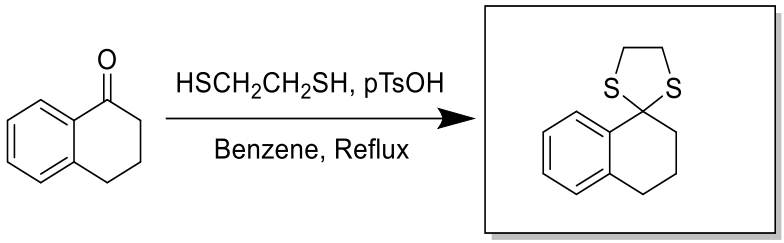
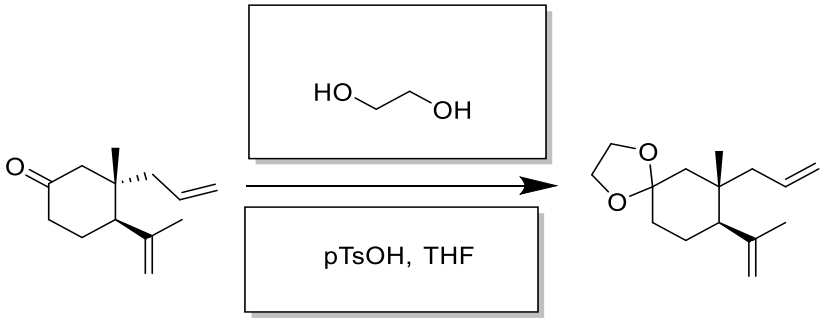
8a.1.23



Dhankhar, J.; Hofer, M. D.; Linden, A.; Čorić, I. Site-Selective C-H Arylation of Diverse Arenes Ortho to Small Alkyl Groups. *Angew. Chem. Int. Ed.* **2022**, *61* (39), e202205470. https://doi.org/10.1002/anie.202205470

8a.1.24



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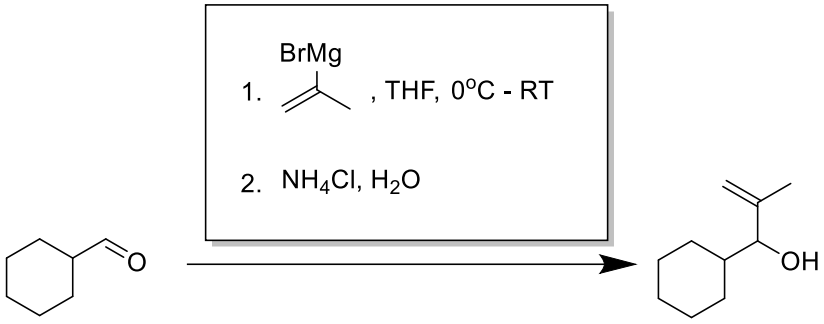
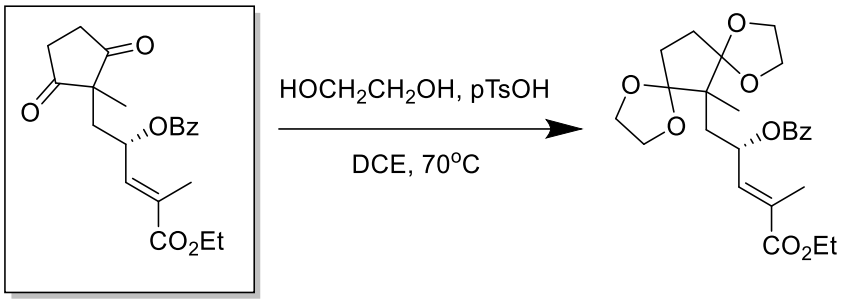
8a.1.25



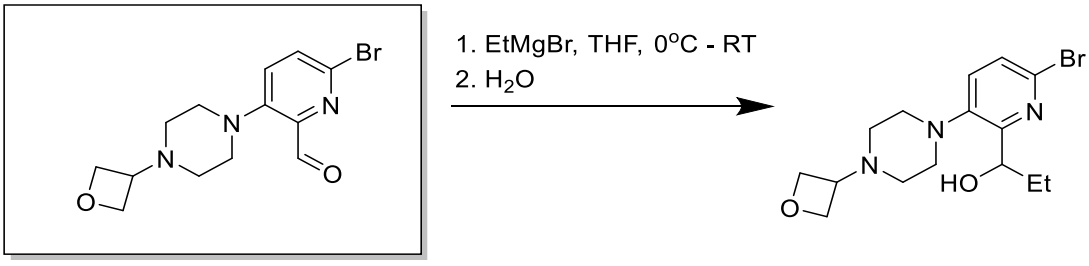
Han, Y.-F.; Hua, K.; Zhao, X.; Li, J.-H. Stereoselective Synthesis of (*E*)-Allylic Sulfones by Photocatalytic Desilyloxylative Sulfonylation of Allyl Silyl Ethers with Thiosulfonates. *Org. Lett.* **2026**, *28* (18), 5698–5703. https://doi.org/10.1021/acs.orglett.6c01026

8a.1.26



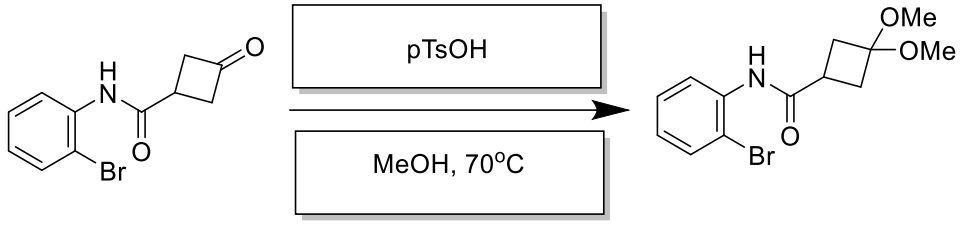
Ikeuchi, K.; Haraguchi, S.; Fujii, R.; Yamada, H.; Suzuki, T.; Tanino, K. Total Synthesis of (+)-Coriamyrtin via a Desymmetrizing Strategy Involving a 1,3-Cyclopentanedione Moiety. *Org. Lett.* **2023**, *25* (16), 2751–2755. https://doi.org/10.1021/acs.orglett.3c00249

8a.1.27



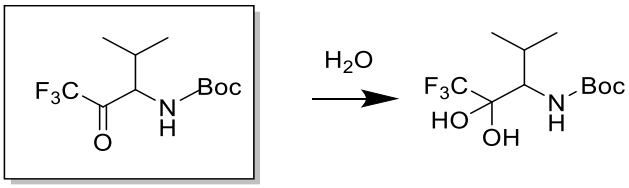
Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2026**, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

8a.1.28



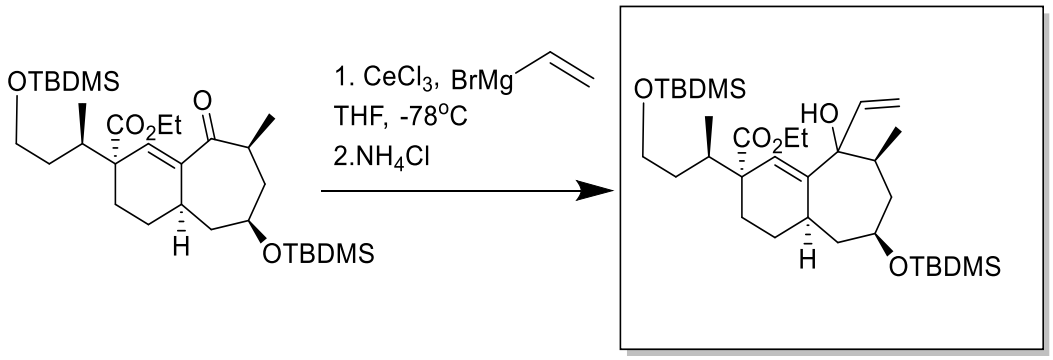
Cao, T. D. C.; Neufeld, K.; Zarate, C.; Nichols, C. J.; Lellek, V.; Deidda, R.; Conza, M.; Schleiss, P.; Rinderhagen, H.; Pye, P.; Muuronen, M.; Chen, W.; Tona, V.; Jouffroy, L.; Viereck, P.; Matcha, K. An Expedient Synthetic Route to the Long-Acting RSV Inhibitor JNJ-6231 via Stereoselective Enzymatic Amination and Regioselective Alkylation. *Org. Process Res. Dev.* **2026**, *30* (1), 121–134. https://doi.org/10.1021/acs.oprd.5c00352

8a.1.29



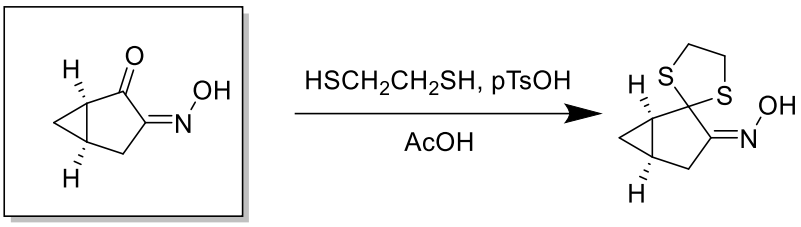
Paszek, K.; Siodła, T.; Janicki, M.; Ludwików, A.; Koroniak, H.; Koroniak-Szejn, K. Toward Novel Trifluoromethylated Peptidomimetics: A Case Study of Cathepsin C Inhibitors. *Eur. J. Org. Chem.* **2026**, *29* (1), e202500773. https://doi.org/10.1002/ejoc.202500773

8a.1.30



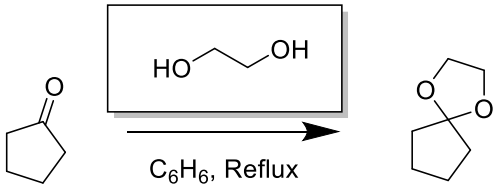
Mao, H.-K.; Wang, Q.; Xu, J. Enantioselective Total Synthesis of Fortalpinoid Q via a $TEMPO^{+}$ BF_4^{-} -Mediated Dehydrative Nazarov Cyclization. *J. Am. Chem. Soc.* **2025**, *147* (11), 9079–9084. https://doi.org/10.1021/jacs.5c00319

8a.1.31



Kadunce, N.; St-Jean, O.; Cagulada, A.; Chang, W.-T. T.; Goldberg, A. F. G.; Huang, Z.; Kang, J.; Kim, J.; Kwon, K.; Lapina, O.; Lin, L.; Rainey, T. J.; Roever, L.; Shah, N. P.; Wolckenhauer, S. A. Synthetic Development and Scale-Up of a Complex Pyrazole Fragment of Lenacapavir. *Org. Process Res. Dev.* **2024**, *28* (8), 3368-3381. https://doi.org/10.1021/acs.oprd.4c00235

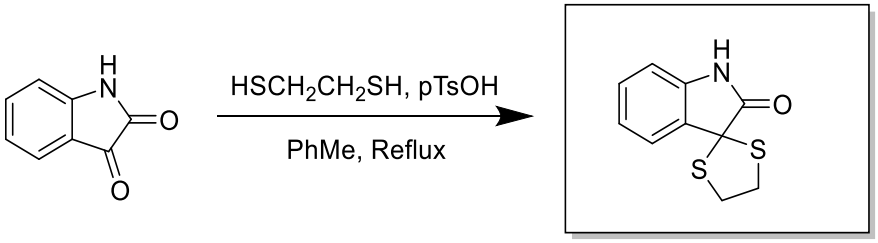
8a.1.32



Note: The authors did not have to use an acid catalyst for this reaction to work.

Bartonek, A.; Klapötke, T. M.; Krumm, B. Sensitive 1,4-Disubstituted Nitro-Containing Cubanes: Structures and Properties. *J. Org. Chem.* **2023**, *88* (18), 12884-12890. https://doi.org/10.1021/acs.joc.3c00384

8a.1.33



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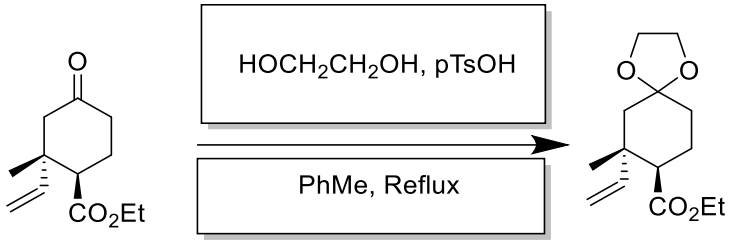
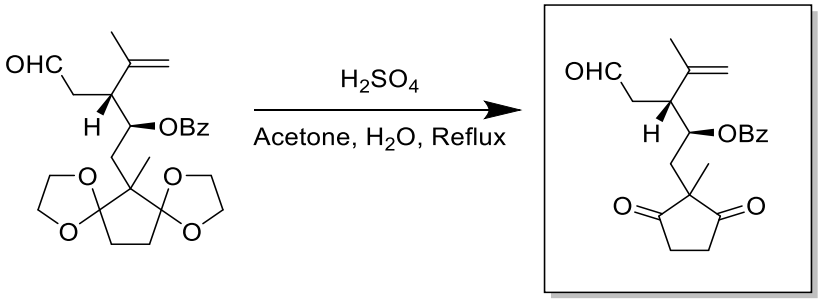
8a.1.34



Yue, G.; Yang, L.; Yuan, C.; Du, B.; Liu, B. Total Syntheses of Lindenane-Type Sesquiterpenoids: (±)-Chloranthalactones A, B, F, (±)-9-Hydroxy Heterogorgiolide, and (±)-Shizukanolide E. *Tetrahedron* **2012**, *68* (47), 9624–9637. https://doi.org/10.1016/j.tet.2012.09.053

8a.1.35

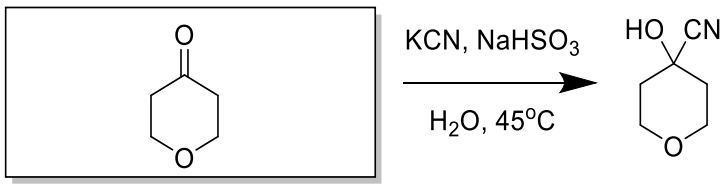


Ikeuchi, K.; Haraguchi, S.; Fujii, R.; Yamada, H.; Suzuki, T.; Tanino, K. Total Synthesis of (+)-Coriamyrtin via a Desymmetrizing Strategy Involving a 1,3-Cyclopentanedione Moiety. *Org. Lett.* **2023**, *25* (16), 2751–2755. https://doi.org/10.1021/acs.orglett.3c00249

Section 8b – Box-Type Questions

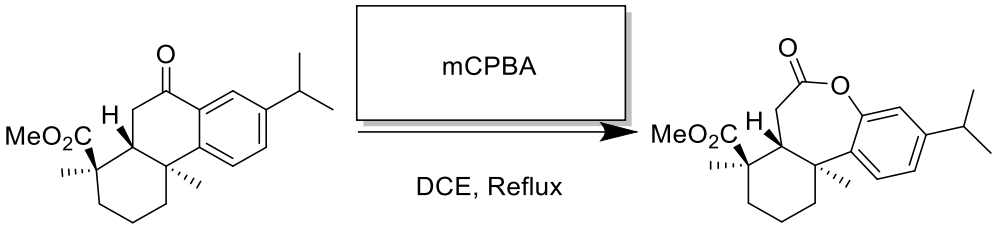
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

8b.1.1



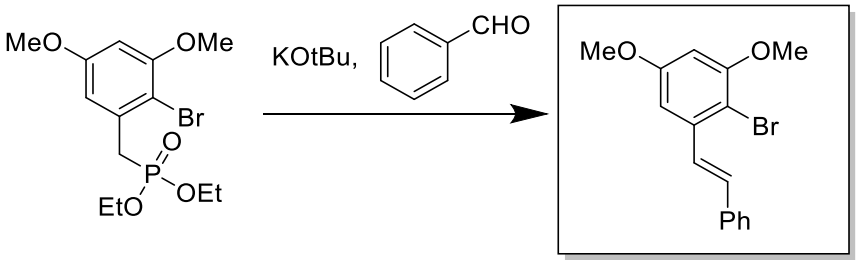
Holovko-Kamoshenkova, O.; Tošner, Z.; Císařová, I.; Hrdina, R. C–H Amination of Enolizable and Nonenolizable Ketones. *Org. Biomol. Chem.* **2025**, *23* (12), 2818–2822. https://doi.org/10.1039/D5OB00009B

8b.1.2



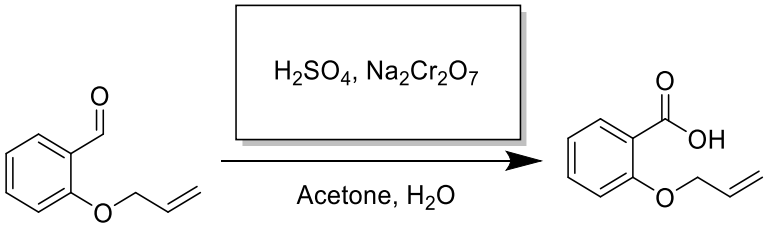
Ikonnikova, V. A.; Solyev, P. N.; Al Mufti, A. M.; Kungurtsev, K. D.; Korlyukov, A. A.; Baranov, M. S.; Mikhaylov, A. A. Synthesis of Chroman Derivatives by Group Transposition and Atom Swapping in 1-Tetralones: Single-Atom Editing Enabled by Oxidative Ring Contraction of Benzoxepine Silyl Ketene Acetals. *Angew. Chem. Int. Ed.* **2025**, *64* (31), e202506564. https://doi.org/10.1002/anie.202506564

8b.1.3



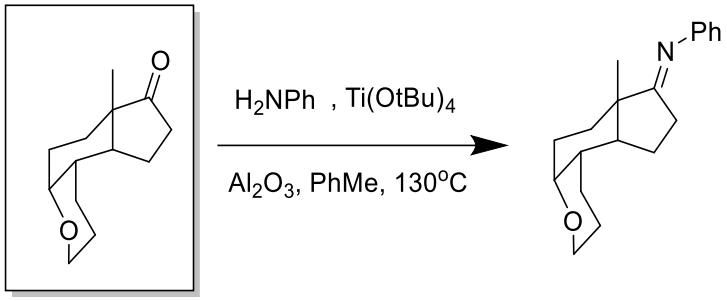
Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. Total Synthesis of Diverse Carbogenic Complexity within the Resveratrol Class from a Common Building Block. *J. Am. Chem. Soc.* **2009**, *131* (5), 1753–1765. https://doi.org/10.1021/ja806183r

8b.1.4



Cheng, Y. A.; Chen, T.; Tan, C. K.; Heng, J. J.; Yeung, Y.-Y. Efficient Medium Ring Size Bromolactonization Using a Sulfur-Based Zwitterionic Organocatalyst. *J. Am. Chem. Soc.* **2012**, *134* (40), 16492-16495. https://doi.org/10.1021/ja307210n

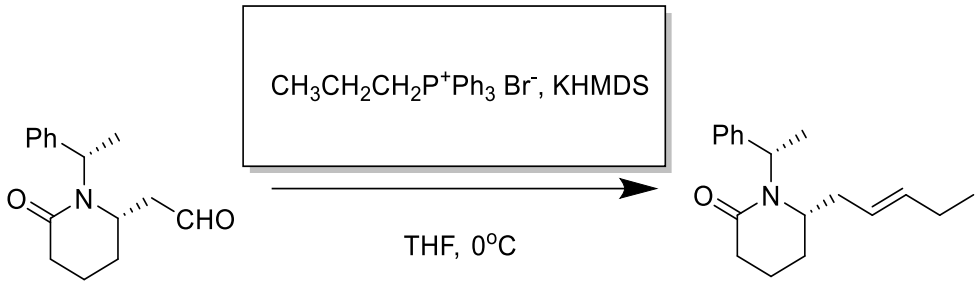
8b.1.5



Hint: Ti(Ot-Bu)$_4$ is used to supply a Lewis acid.

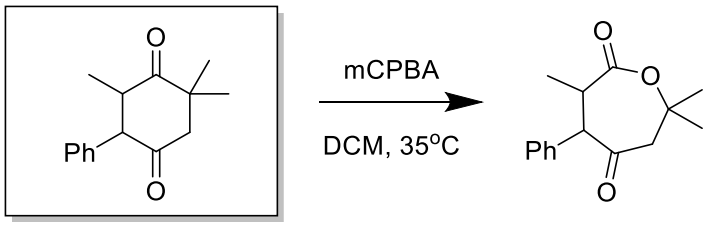
Wu, L.; McIntyre, B. N.; Wu, S.; Jiao, Z.; Fox, C. B.; Schley, N. D.; Schuppe, A. W. Photocatalyzed Epimerization of Quaternary Stereocenters. *J. Am. Chem. Soc.* **2025**, *147* (13), 11080-11088. https://doi.org/10.1021/jacs.4c16769

8b.1.6



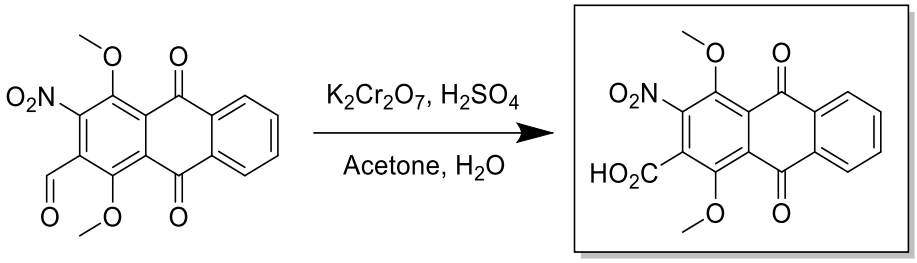
Nishikawa, K.; Ono, Y.; Mori, S.; Takayama, K.; Ihara, M.; Matsuda, K.; Morimoto, Y. Divergent Nine-Step Syntheses of Perhydrohistrionicotoxin Analogs and Their Inhibition Activity Toward Chicken A4β2-Neuronal Nicotinic Acetylcholine Receptors. *J. Org. Chem.* **2024**, *89* (6), 4128–4133. https://doi.org/10.1021/acs.joc.3c02988

8b.1.7



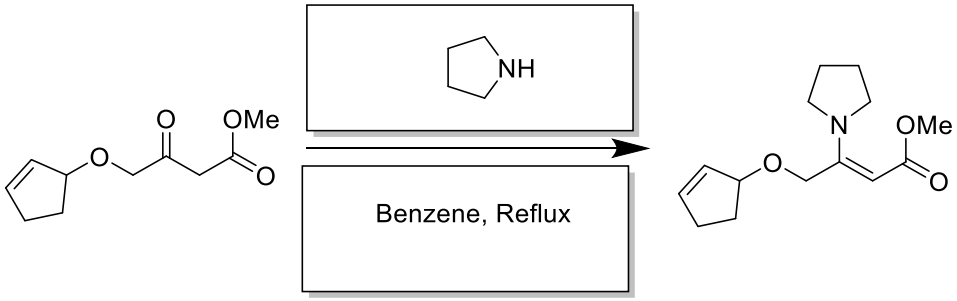
Xiong, J.; Wang, Y.; Tang, X. Binaphthalene-Modified *C* -Scorpionate Zinc Catalysts for Ring-Opening Polymerization of Bio-Based *γ* -Ketolactones to High-Molar-Mass Degradable Polyesters. *Angew. Chem. Int. Ed.* **2026**, *65* (3), e17535. https://doi.org/10.1002/anie.202517535

8b.1.8



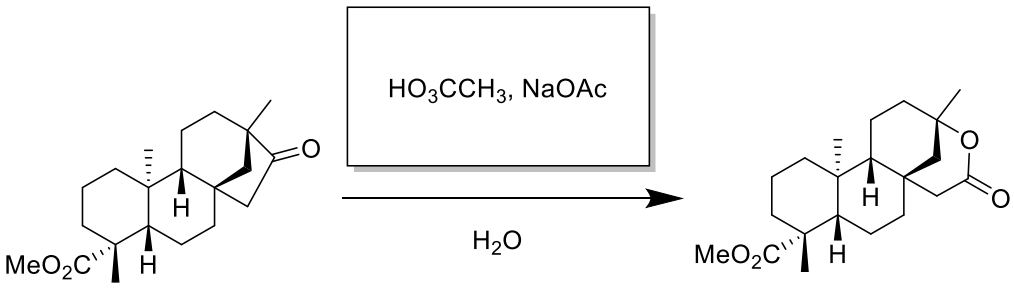
Litvinova, V. A.; Gostev, A. S.; Tikhomirov, A. S.; Shchekotikhin, A. E. New Heteroarene-Fused Anthraquinones: Synthesis and PyBOP-Mediated Amination. *Tetrahedron* **2023**, *149*, 133722. https://doi.org/10.1016/j.tet.2023.133722

8b.1.9



Ho, G.-M.; Tseng, C.-W.; Liu, Y.-H.; Li, Y.-J. Direct Synthesis of 5-Cycloalkene-Substituted γ-Butenolides via [2,3]-Wittig Rearrangement of Vinylogous Urethanes. *Synth. Commun.* **2026**, *56* (4), 318-327. https://doi.org/10.1080/00397911.2026.2621827

8b.1.10



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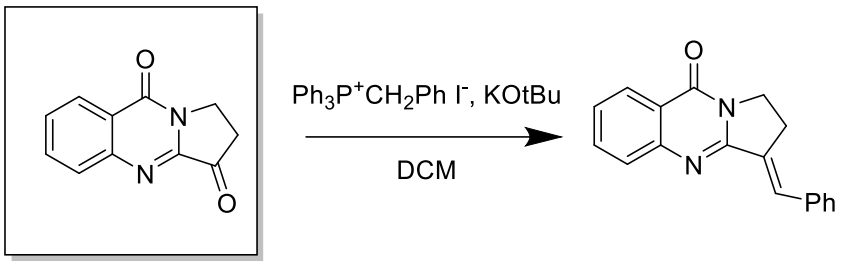
8b.1.11



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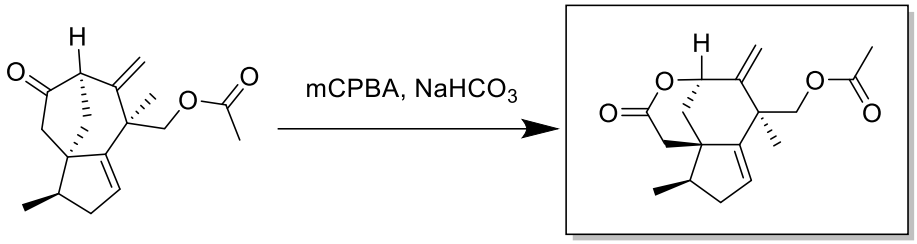

Fu, P.; Liu, T.; Shen, Y.; Lei, X.; Xiao, T.; Chen, P.; Qiu, D.; Wang, Z.; Zhang, Y. Divergent Total Syntheses of Illicium Sesquiterpenes through Late-Stage Skeletal Reorganization. *J. Am. Chem. Soc.* **2023**, *145* (33), 18642-18648. https://doi.org/10.1021/jacs.3c06442

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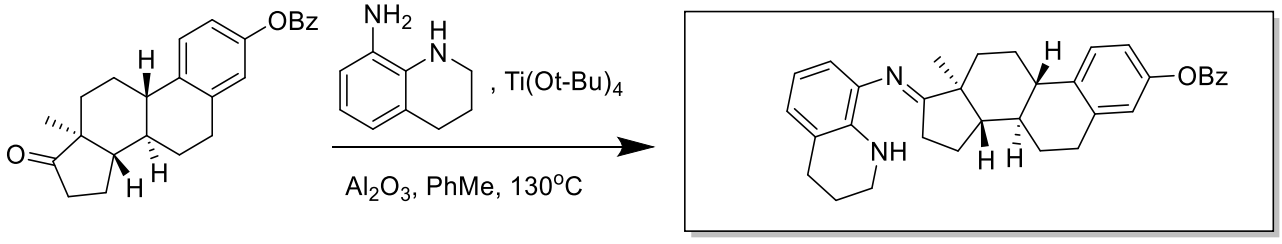

Hint: $Ti(Ot\text{-}Bu)_4$ is a Lewis acid.

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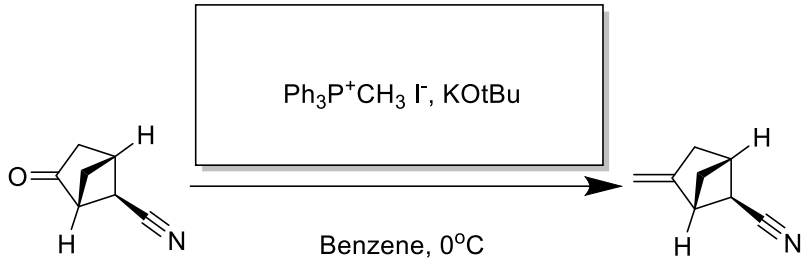

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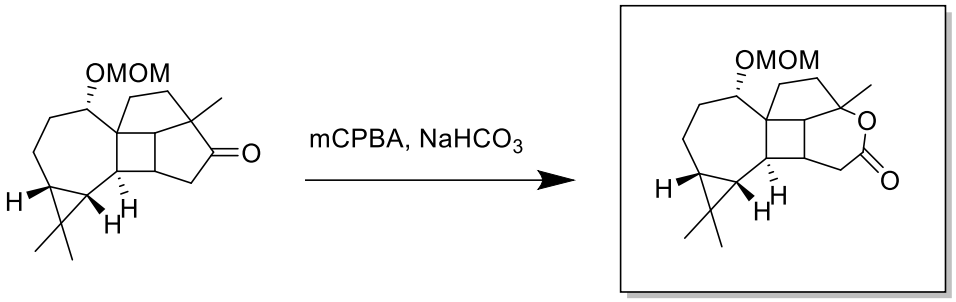

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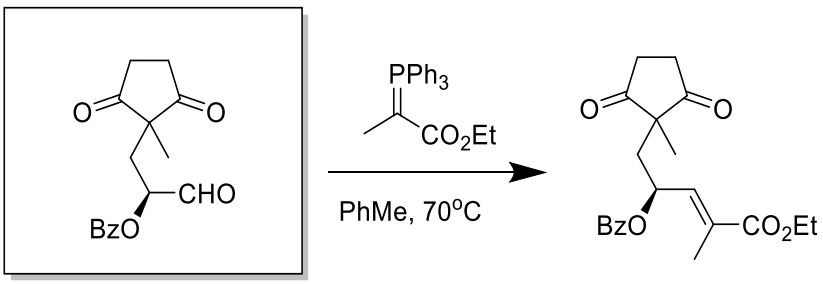
8b.1.16



Kuwabara, M.; Matsuo, A.; Kamo, S.; Matsuzawa, A.; Sugita, K. Stereoselective Convergent Synthesis of Carbon Skeleton of Cotylenin A Aglycone. *Synthesis* **2021**, *53* (12), 2092–2102. https://doi.org/10.1055/s-0040-1706684

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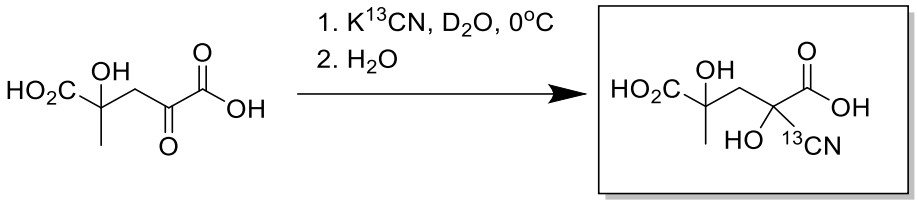

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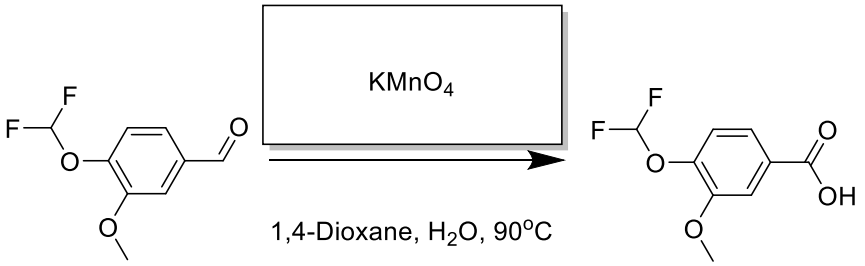

Mungalpara, M. N.; Wu, X.; Ma, X.; Zhu, Z.; Jiang, M.; Pike, V. W.; Lu, S.; Zhang, H.; Wu, Z.; Kinon, P. O.; Huang, Y.; Nicewicz, D. A.; Li, Z. Deoxyradiofluorination of Phenols via a Difluoromethoxy Nucleofuge Enabled by Organic Photoredox Catalysis. *ACS Cent. Sci.* **2026**, *12* (5), 638–648. https://doi.org/10.1021/acscentsci.6c00127

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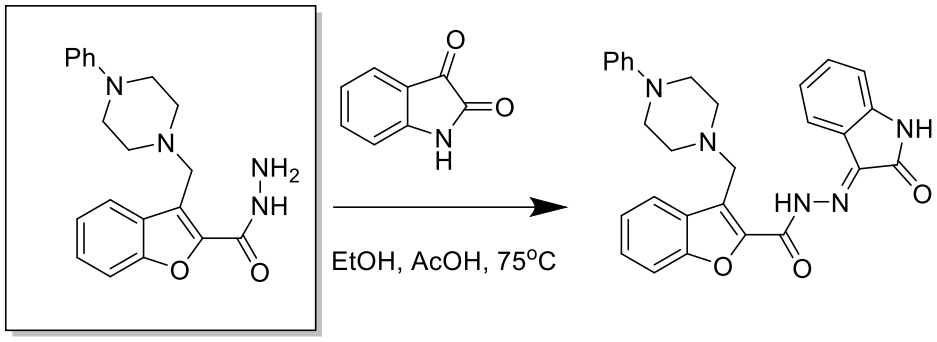

Eldehna, W. M.; Tawfik, H. O.; Nafie, M. S.; Al Kamaly, O.; El-Hamaky, A. A.; El Hassab, M. A.; Elsayed, Z. M.; Elnaggar, Y. S. R.; Al-Karmalawy, A. A.; Di Giacomo, V.; Balaha, M. Novel Benzofuran-Conjugated Indolin-2-ones as Anticancer Agents: Design, Synthesis, Biological Assessments, and Molecular Modeling Insights. *Bioorg. Chem.* **2025**, *160*, 108494. https://doi.org/10.1016/j.bioorg.2025.108494

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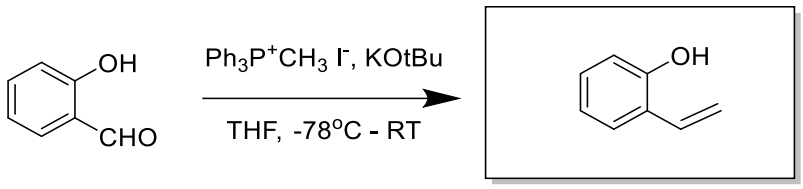

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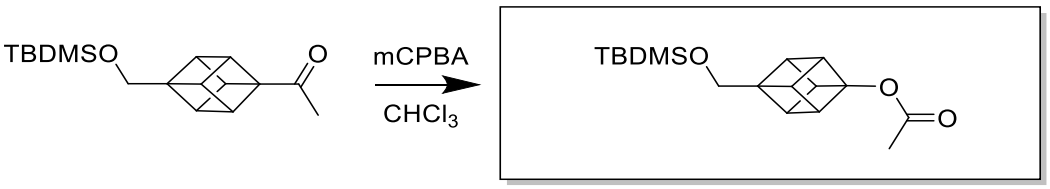

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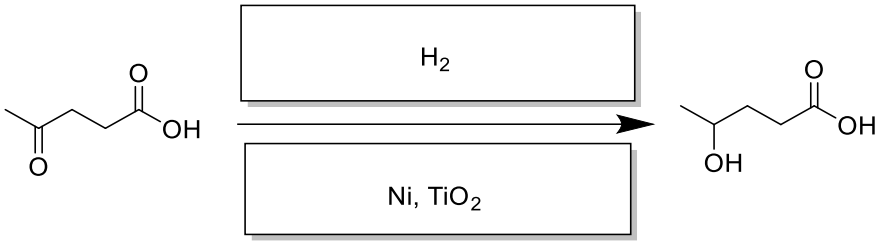
8b.1.22



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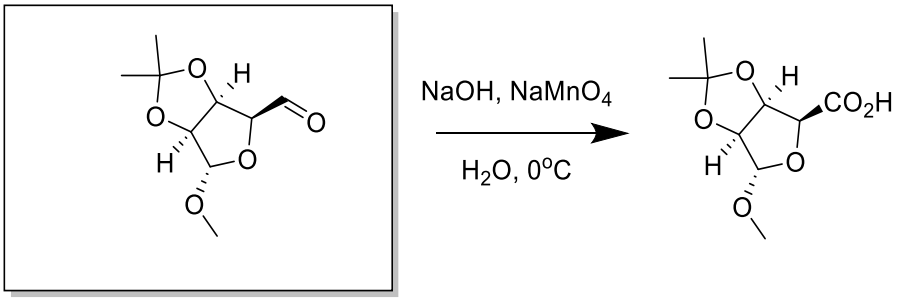

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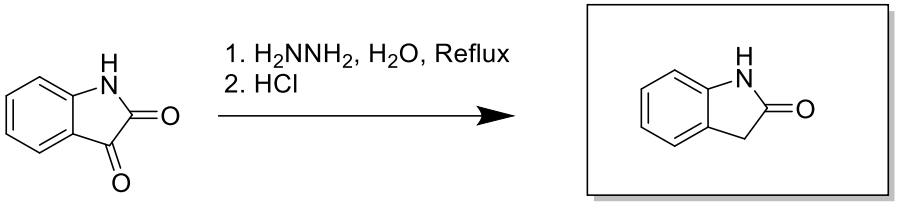

Note: Although the conditions in step 2 are acidic and you would typically learn that this reaction occurs under basic conditions, please assume they lead to the same product.

Yousefian, M.; Hashemi, M.; Eskandarpour, V.; Zarghi, A.; Hadizadeh, F.; Ghodsi, R. New Indolin-2-ones, Possessing Sunitinib Scaffold as HDAC Inhibitors and Anti-Cancer Agents with Potential VEGFR Inhibition Activity: Design, Synthesis and Biological Evaluation. *Bioorg. Chem.* **2025**, *156*, 108231. https://doi.org/10.1016/j.bioorg.2025.108231

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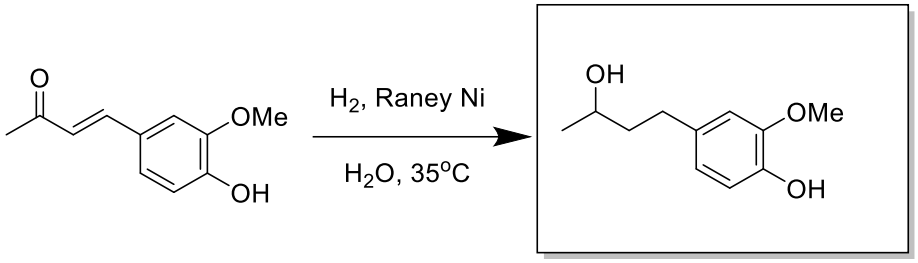

Zhang, Y.; Fayad, E.; Katouah, H. A.; Qin, H.-L. Solvent-Controlled and Highly Chemoselective Reduction of α,β-Unsaturated Ketones and Aldehydes. *J. Org. Chem.* **2025**, *90* (16), 5704–5709. https://doi.org/10.1021/acs.joc.5c00151

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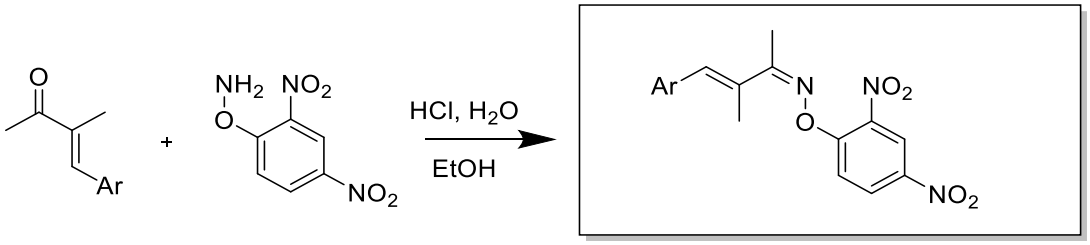

Zeng, Q.-Y.; Zhang, Y.-Q.; Cheng, X.-Y.; Xu, H.; Dai, H.-X. Synthesis of Polysubstituted Pyrroles via (2 + 2 + 1) Cyclization of Enone Oxime Ethers with Alkynes and Diaziridinone. *J. Org. Chem.* **2026**, *91* (3), 1271–1275. https://doi.org/10.1021/acs.joc.5c01879

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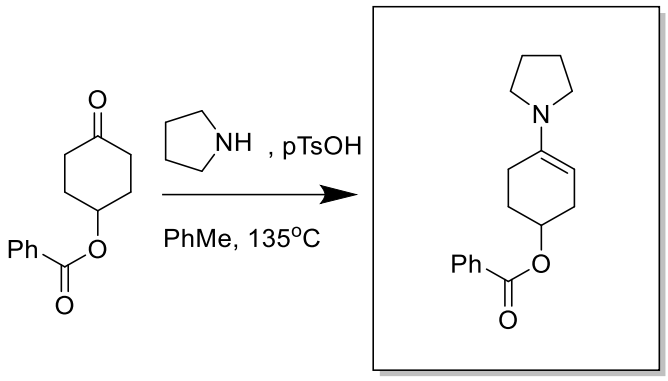
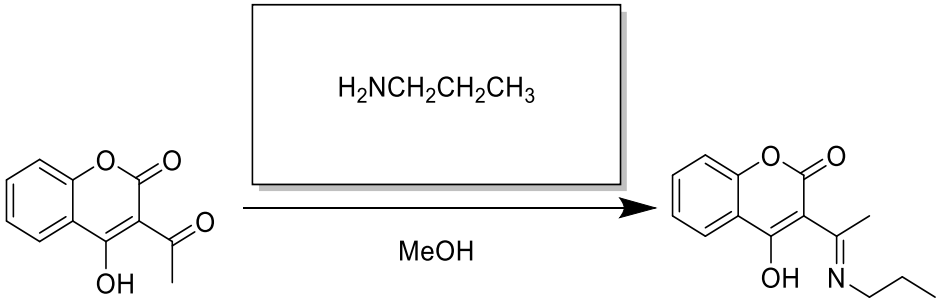


Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in Sp^3 -Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536–542. https://doi.org/10.1126/science.aef0610

8b.1.28



Aarjane, M.; Slassi, S.; Ait Mouha, M.; El-Ghayoury, A.; Yamni, K.; Amine, A. A New Coumarin Derivative: Synthesis, Crystal Structure, Computational Studies, and Dual Antioxidant–Antibacterial Activity. *J. Mol. Struct.* **2026**, *1349*, 143839. https://doi.org/10.1016/j.molstruc.2025.143839

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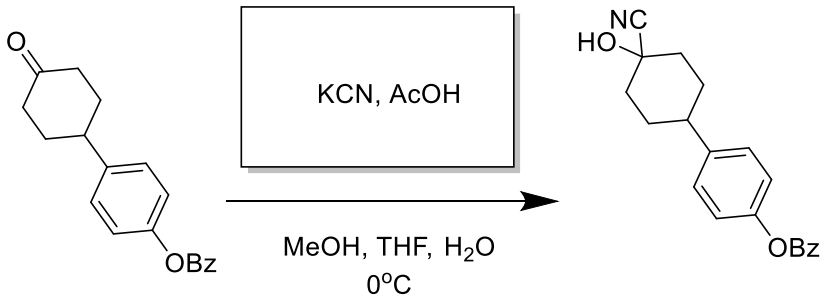

Amatya, E.; Subramanian, C.; Long, R.; McNamara, K.; Cohen, M. S.; Blagg, B. S. J. The Investigation of Hsp90C-Terminal Inhibitors Containing Amide Bioisosteres. *ChemMedChem* **2024**, *19* (24), e202400418. https://doi.org/10.1002/cmdc.202400418

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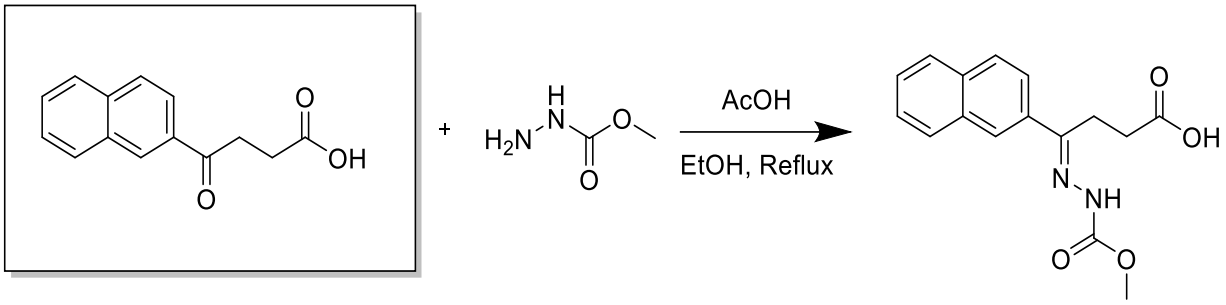
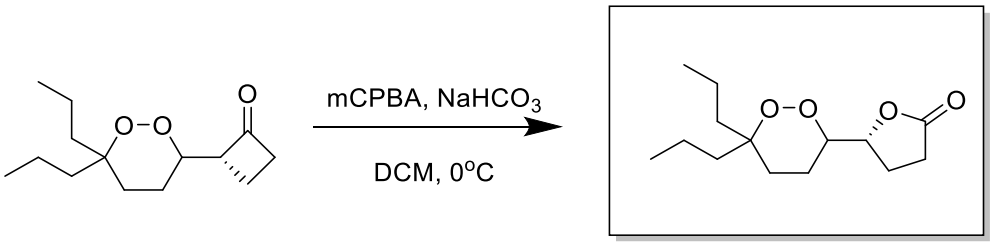


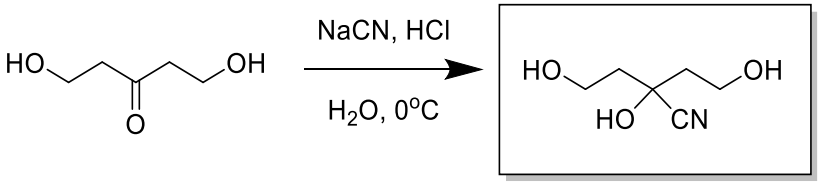
Cranwell, P. B.; Russell, A.; Smith, C. Methyl Hydrazinocarboxylate as a Practical Alternative to Hydrazine in the Wolff-Kishner Reaction. *Synlett* **2016**, *27* (1), 131-135. https://doi.org/10.1055/s-0035-1560805

8b.1.31



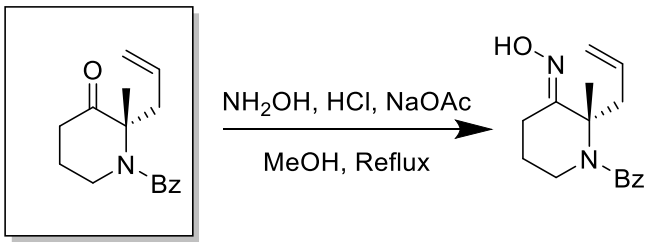
Champciaux, B.; Jamey, N.; Figadère, B.; Ferrié, L. Peroxycarbenium-Mediated Asymmetric Synthesis of 1,2-Dioxanes and 1,2-Dioxolanes. *J. Am. Chem. Soc.* **2025**, *147* (4), 3353–3359. https://doi.org/10.1021/jacs.4c13899

8b.1.32



Yerabolu, J. R.; Liotta, C. L.; Krishnamurthy, R. Anchimeric-Assisted Spontaneous Hydrolysis of Cyanohydrins Under Ambient Conditions: Implications for Cyanide-Initiated Selective Transformations. *Chem. Eur. J.* **2017**, *23* (36), 8756–8765. https://doi.org/10.1002/chem.201701497

8b.1.33

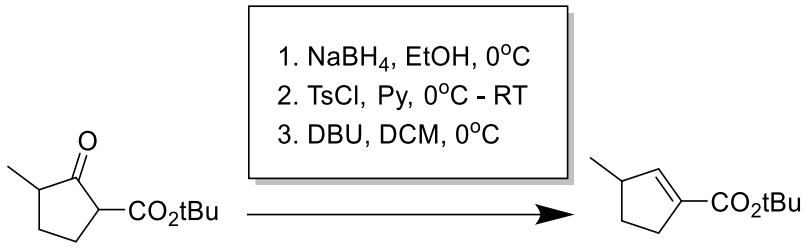


Wang, Z.; Chen, D.; Chang, J.; Li, Y.; Su, Y.; Tang, P.; Chen, F.-E. Enantioselective Synthesis of Functionalized 2,2-Disubstituted Piperidines Enabled by Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation. *Org. Lett.* **2026**, *28* (2), 794–799. https://doi.org/10.1021/acs.orglett.5c04932

Section 9: Multi-Step Synthesis 1

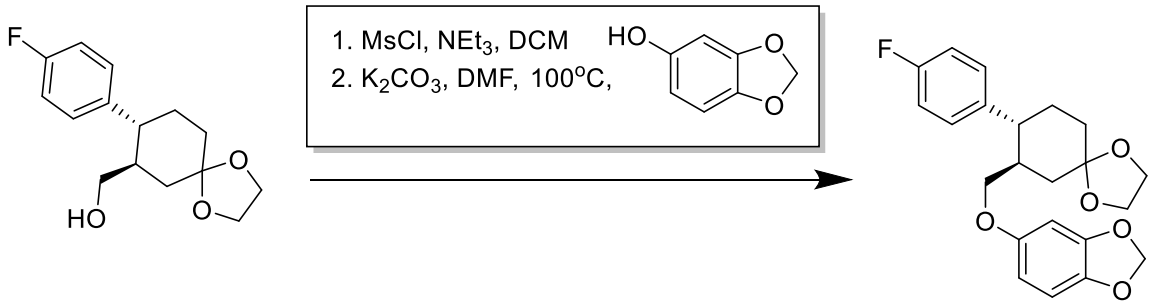
The multistep syntheses presented in this section draw upon fundamental concepts and reactions in Sections 1-8. For each of the questions below, provide reagents that would produce the product indicated from the starting material.

9.1



Bunnage, M. E.; Chippindale, A. M.; Davies, S. G.; Parkin, R. M.; Smith, A. D.; Withey, J. M. Asymmetric Synthesis of (1R,2S,3R)-3-Methylcispentacin and (1S,2S,3R)-3-Methyltranspentacin by Kinetic Resolution of *tert*-Butyl (±)-3-Methylcyclopentene-1-carboxylate. *Org. Biomol. Chem.* **2003**, *1* (21), 3698-3707. https://doi.org/10.1039/B306935B

9.2



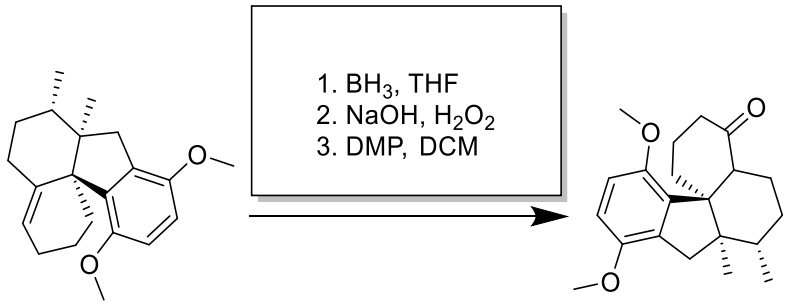
Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in *sp*^{3}-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

9.3



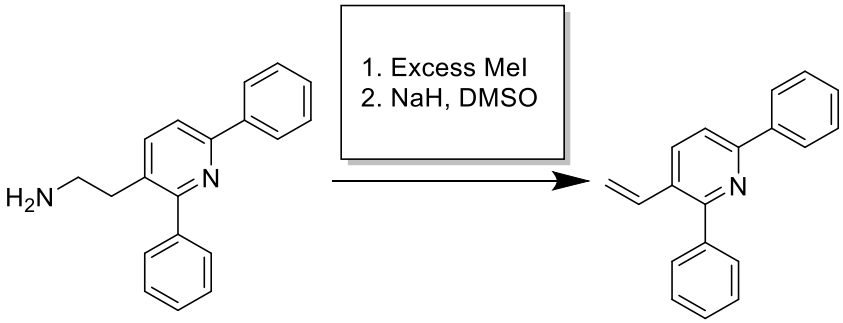
Belov, D. S.; Lukyanenko, E. R.; Kurkin, A. V.; Yurovskaya, M. A. Highly Stereoselective and Scalable Synthesis of *Trans* -Fused Octahydrocyclohepta[*b*]Pyrrol-4(1 *H*)-Ones via the Aza-Cope–Mannich Rearrangement in Racemic and Enantiopure Forms. *J. Org. Chem.* **2012**, *77* (22), 10125–10134. https://doi.org/10.1021/jo301762a

9.4



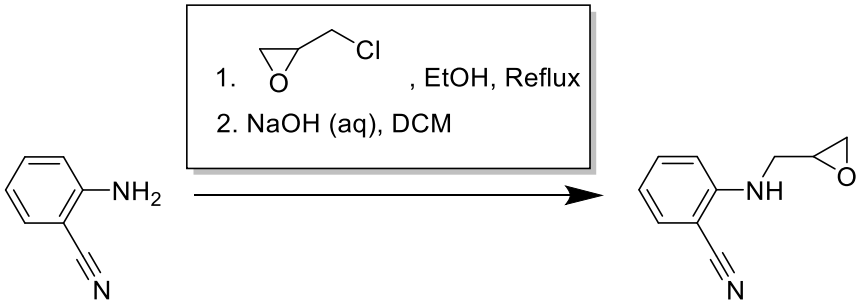
Chong, C.; Chang, L.; Grimm, I.; Zhang, Qunlong; Kuang, Y.; Wang, B.; Kang, J.; Liu, W.; Baars, J.; Guo, Y.; Schmalz, H.-G.; Lu, Z. Divergent Total Synthesis of the Revised Structures of Marine Anti-Cancer Meroterpenoids (+)-Dysiherbols A-E. *Chem. Sci.* **2023**. *14* (12). 3302-3310. https://doi.org/10.1039/d3sc00173c

9.5



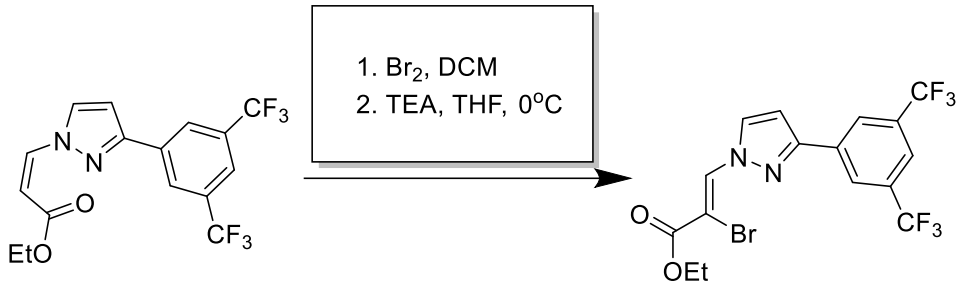
Khardina, P. A.; Buev, E. M.; Moshkin, V. S.; Sosnovskikh, V. Y. Four-Step Synthesis of the β-Pyridylethylamine Core via Ring Opening of Pyrrolidines. *J. Org. Chem.* **2026**, *91* (18), 6279-6293. https://doi.org/10.1021/acs.joc.5c03267

9.6



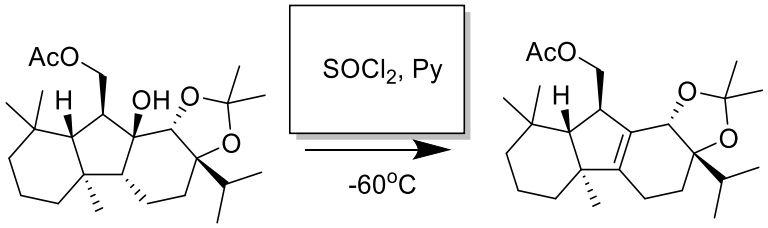
Lee, K.; Lee, X.; Zhou, C.-Y.; Chu, Y.-L.; Lin, C.-K. *Tert* -Butyl Carbonate as a Nucleophile in Epoxide Ring Opening: A Cascade Synthesis of 5-(Hydroxymethyl)Oxazolidin-2-One. *J. Org. Chem.* **2025**, *90* (23), 7976–7981. https://doi.org/10.1021/acs.joc.5c00537

9.7



Miao, H.; Qin, Y.; Shao, D.; Chen, Q.; Pan, Y.; Lei, M.; Wu, R.; Ye, X.; Wang, X.; Zhu, Y. Discovery of SZJK-0421: A Novel Potent, Low Toxicity, Selective Second Generation of CRM1 Inhibitor for the Treatment of Both Hematological and Solid Tumors. *J. Med. Chem.* **2024**, *67* (22), 20595–20618. https://doi.org/10.1021/acs.jmedchem.4c02169

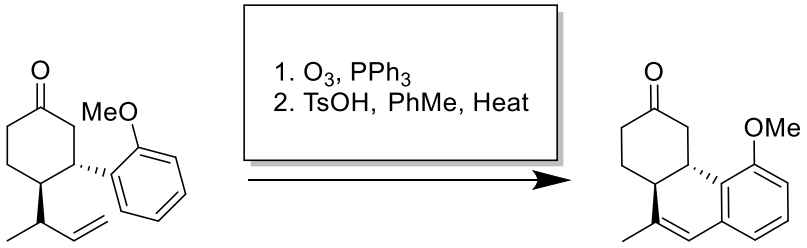
9.8



Note: You will learn later that this structure contains acid-sensitive functional groups, so acidic conditions should be avoided.

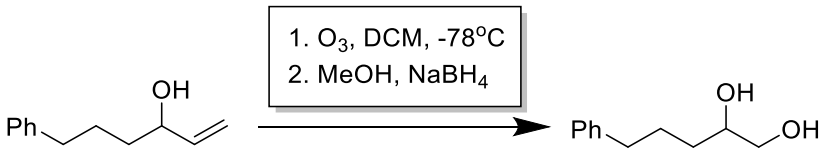
Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. Enantioselective Total Synthesis of Cytotoxic Taiwaniaquinones A and F. *Chem. Commun.* **2010**, *46* (48), 9244. https://doi.org/10.1039/c0cc03763j

9.9



Roosen, P. C.; Karns, A. S.; Ellis, B. D.; Vanderwal, C. D. Evolution of a Short and Stereocontrolled Synthesis of (+)-7,20-Diisocyanoadociane. *J. Org. Chem.* **2022**, *87* (2), 1398–1420. https://doi.org/10.1021/acs.joc.1c02700

9.10



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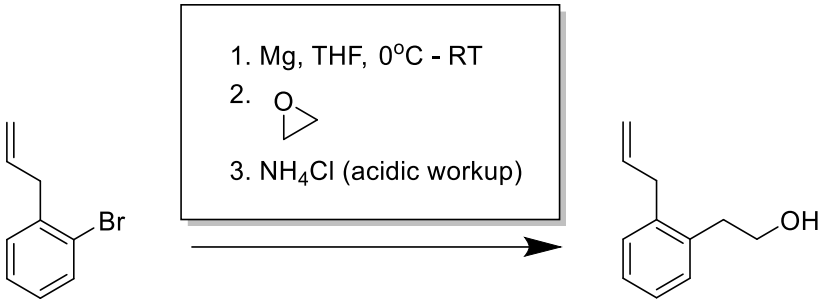
9.11



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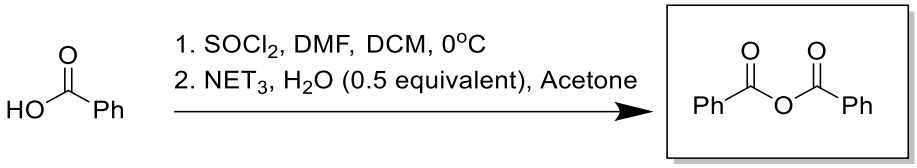
Section 10a – Box-Type Questions

For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

10a.1.1



Herington, F.; Achal, F. J.; Figueroa-Agosto, D.; Liu, C.; Ge, H. Regioselective Pd-Catalyzed C1–H Acylation of Carbazoles via Pd/Norbornene Cooperative Catalysis. *J. Org. Chem*. **2025**, *90* (35), 12485–12489. https://doi.org/10.1021/acs.joc.5c01838

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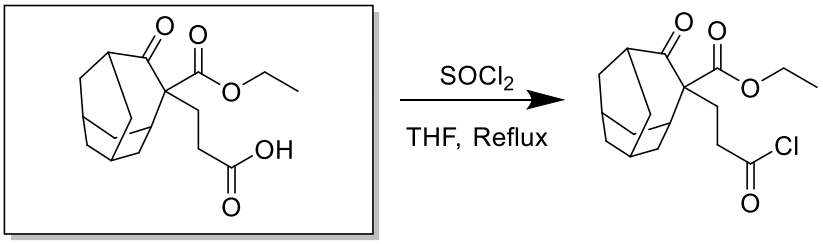

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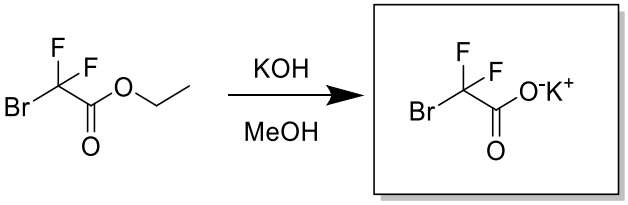

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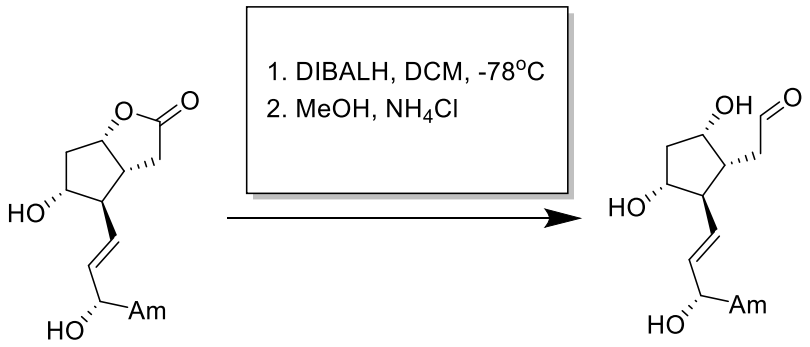

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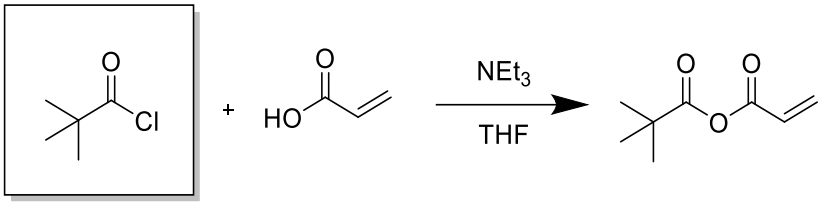

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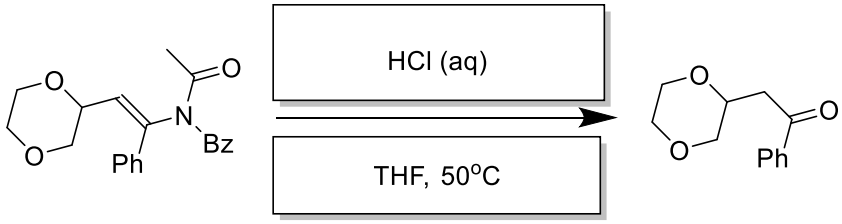

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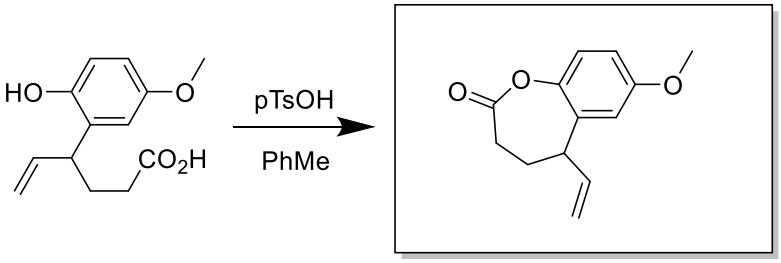

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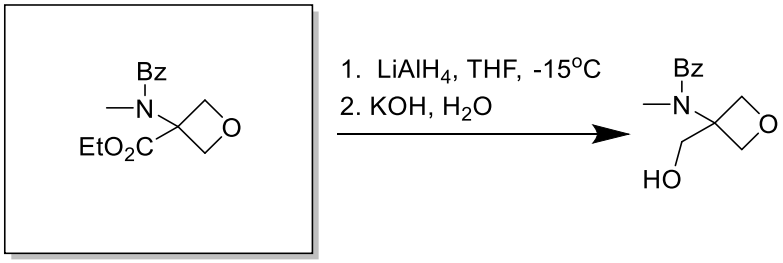

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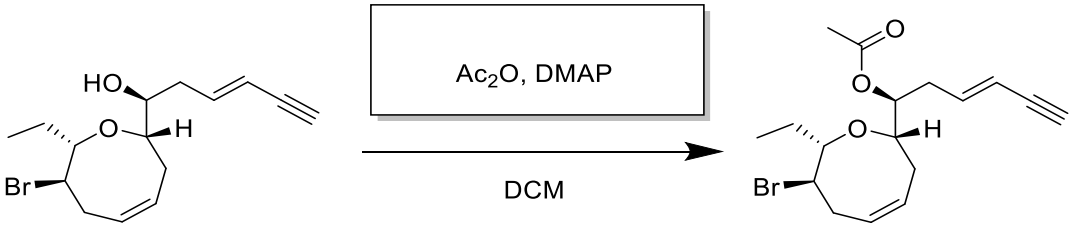

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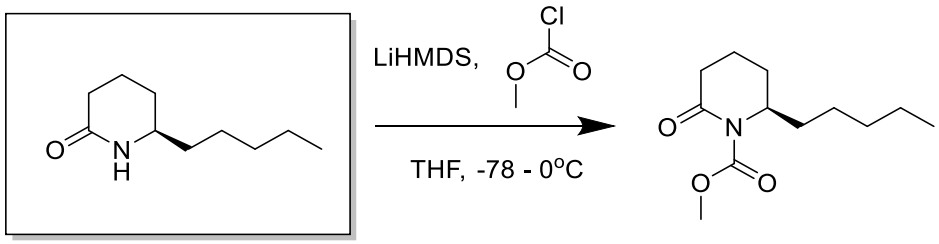

Nishikawa, K.; Ono, Y.; Mori, S.; Takayama, K.; Ihara, M.; Matsuda, K.; Morimoto, Y. Divergent Nine-Step Syntheses of Perhydrohistrionicotoxin Analogs and Their Inhibition Activity Toward Chicken A4β2-Neuronal Nicotinic Acetylcholine Receptors. *J. Org. Chem.* **2024**, *89* (6), 4128–4133. https://doi.org/10.1021/acs.joc.3c02988

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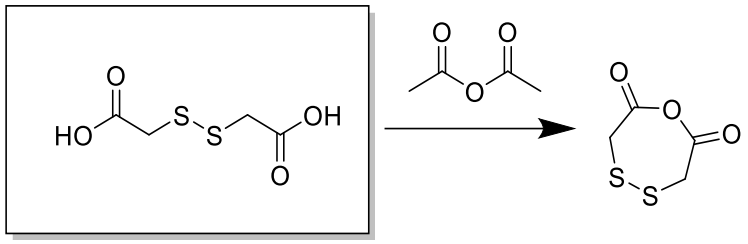

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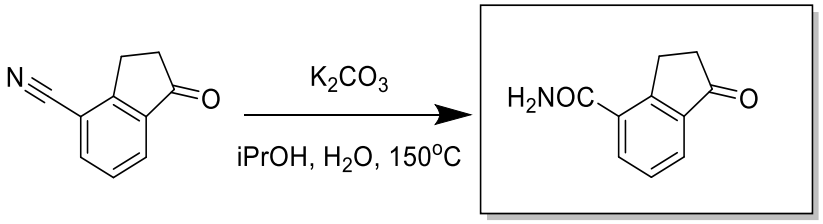

Narayanan, D.; Tran, K. T.; Pallesen, J. S.; Solbak, S. M. Ø.; Qin, Y.; Mukminova, E.; Luchini, M.; Vasilyeva, K. O.; González Chichón, D.; Goutsiou, G.; Poulsen, C.; Haapanen, N.; Popowicz, G. M.; Sattler, M.; Olagnier, D.; Gajhede, M.; Bach, A. Development of Noncovalent Small-Molecule Keap1-Nrf2 Inhibitors by Fragment-Based Drug Discovery. *J. Med. Chem.* **2022**, *65* (21), 14481–14526. https://doi.org/10.1021/acs.jmedchem.2c00830

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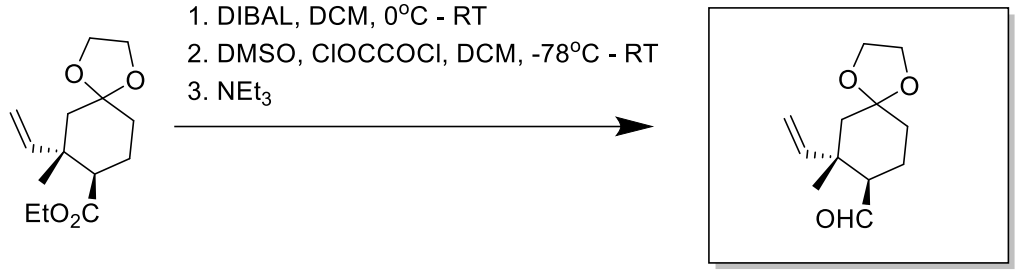

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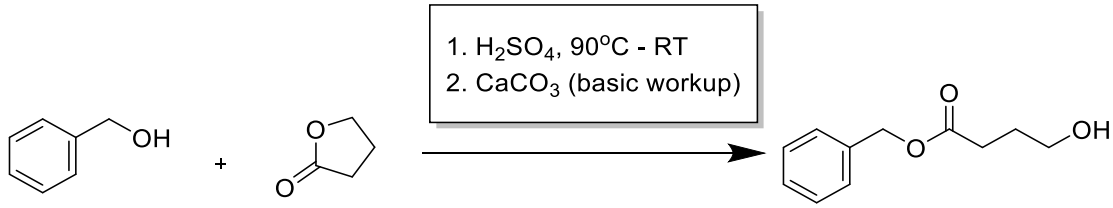

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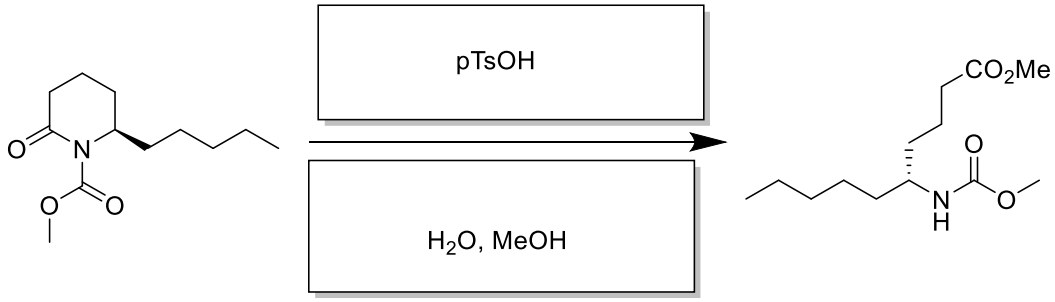

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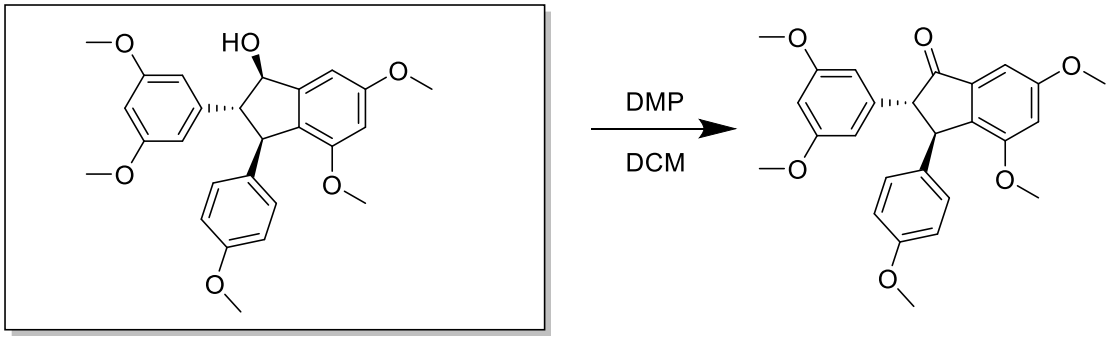

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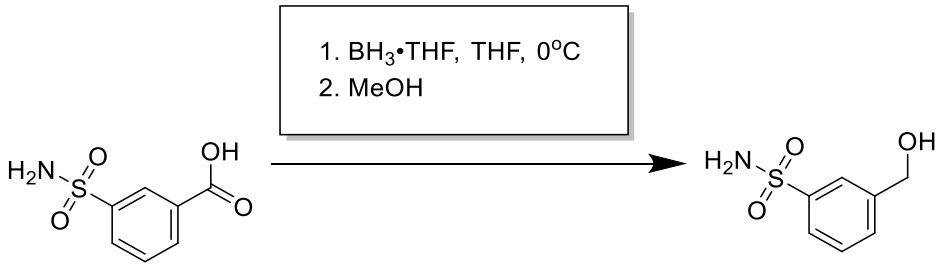

Kong, Y.; Su, M.; Jiang, C.; Feng, H.; Hu, Y.; Li, D.; Mao, Z.; Liu, F.; Zhu, F.; Guo, Y.; Ren, S.; Chi, M.; Qiu, T.; Yuan, Y.; Huang, W.; Ma, L.; Chen, X. Rational Design of an NLRP3 Inhibitor with Superior Efficacy and Safety for Gout Therapy. *Eur. J. Med. Chem.* **2026**, *305*, 118578. https://doi.org/10.1016/j.ejmech.2026.118578

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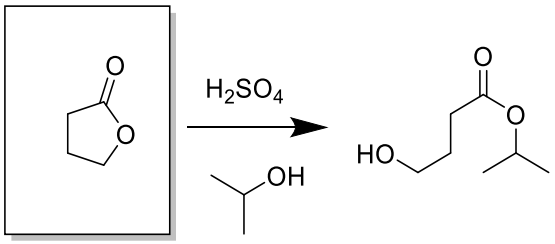

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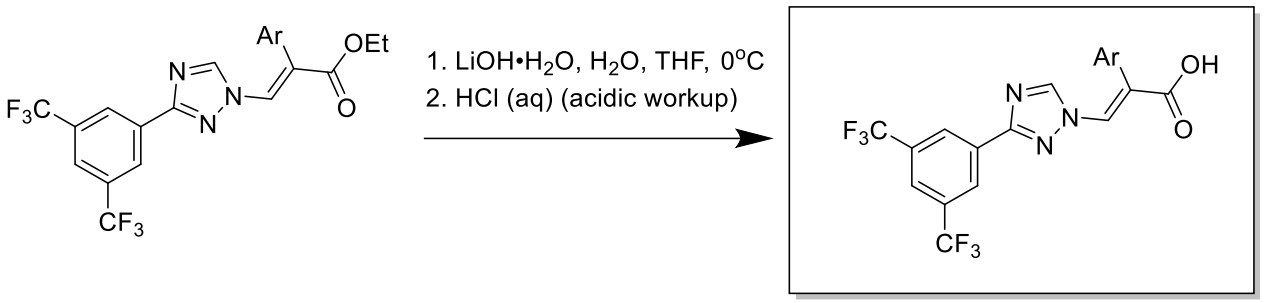

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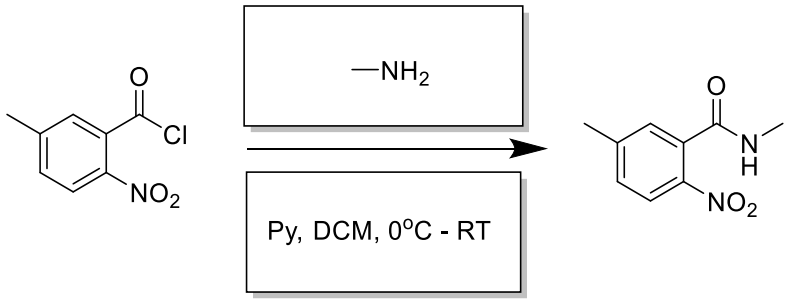

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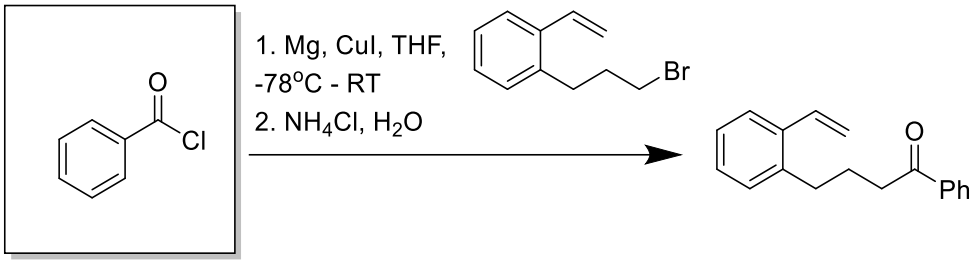

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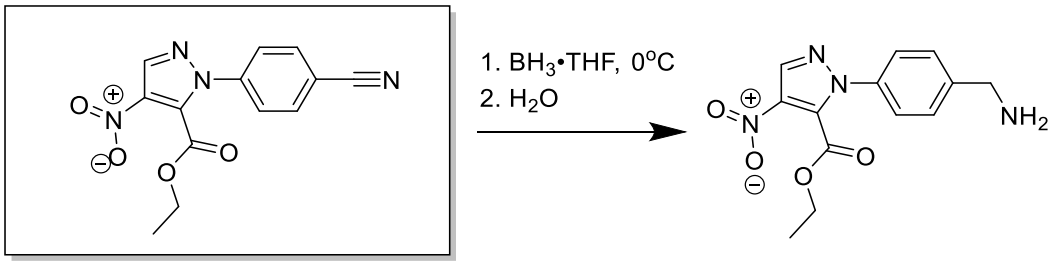

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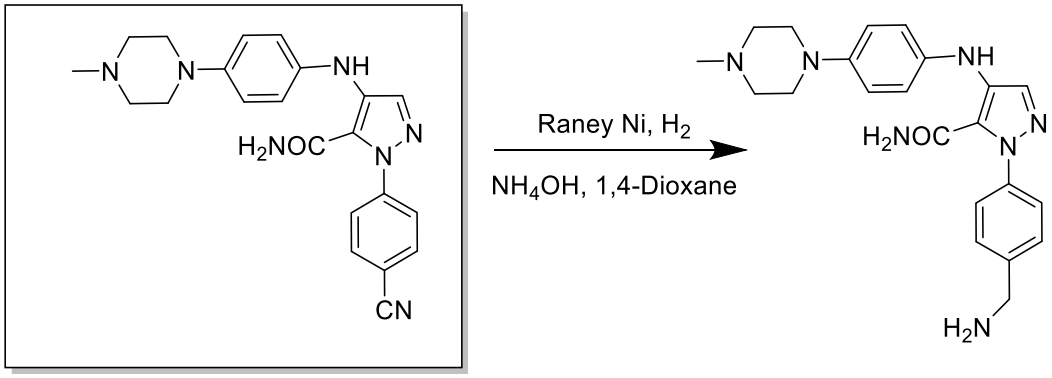

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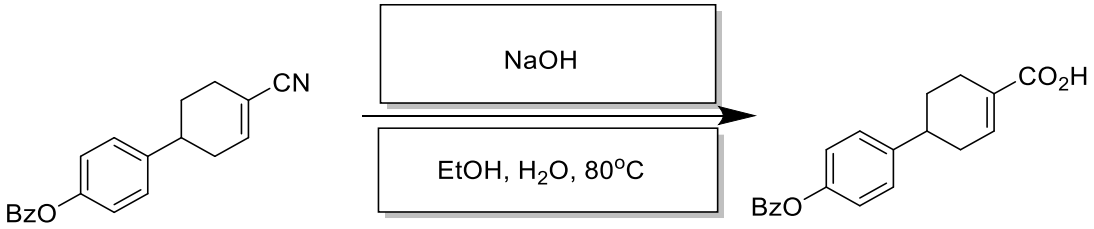

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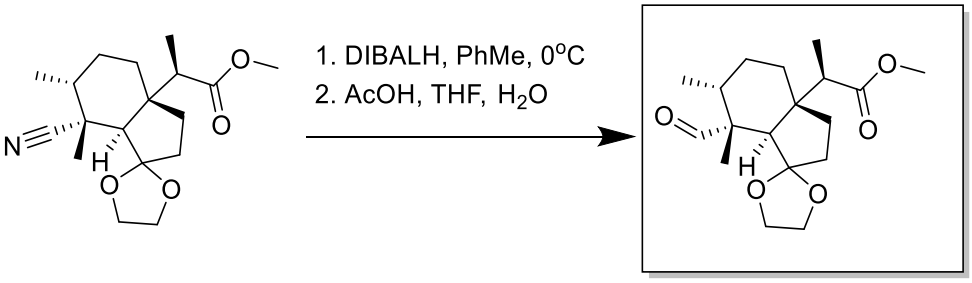

Note: Under the conditions provided, the ester group is not reduced.

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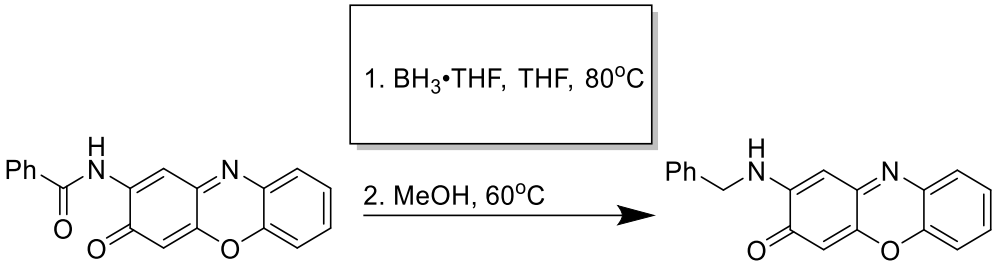

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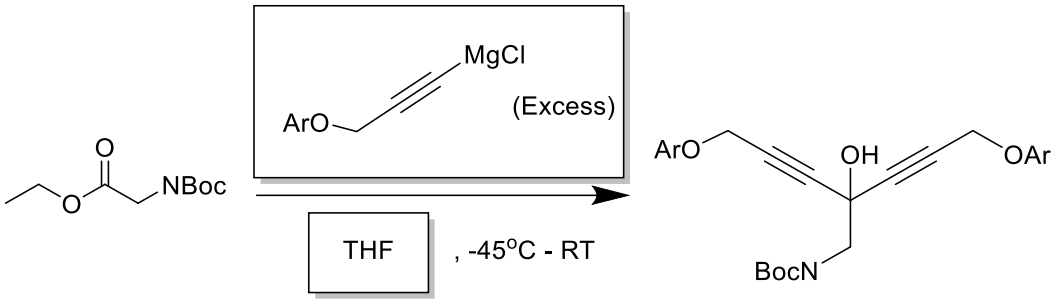

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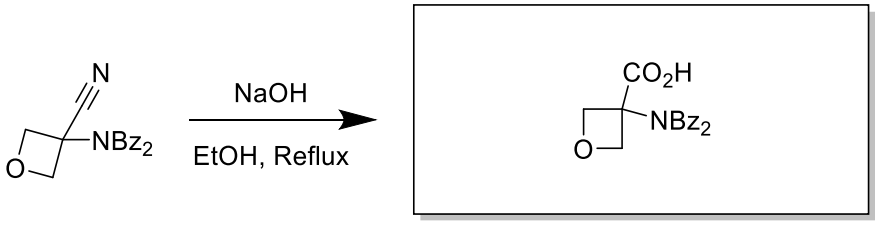

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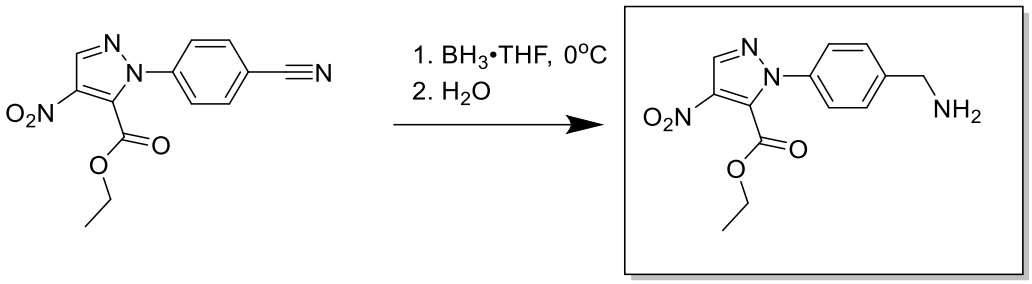
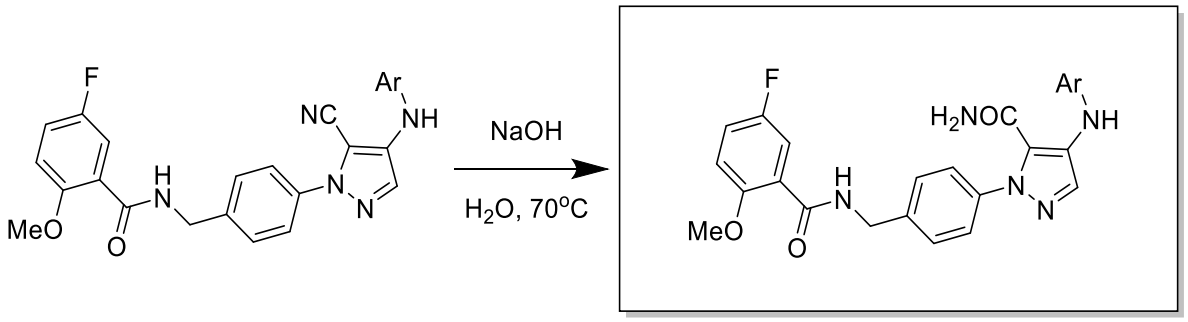


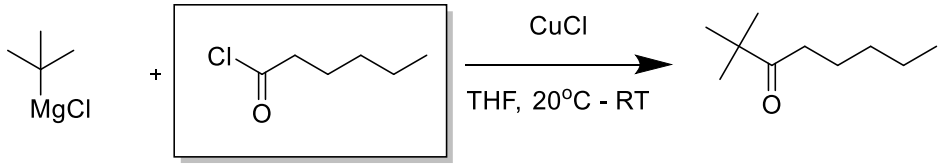
Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2026**, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

10b.1.10



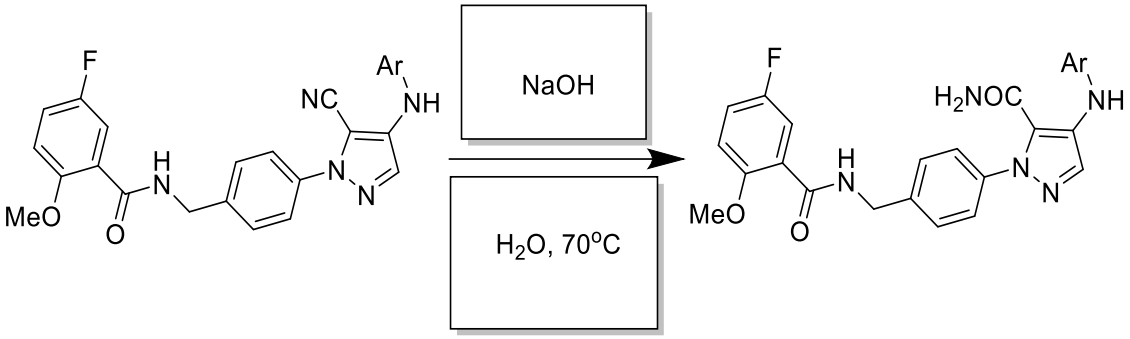
Liu, G.; Liu, S.; Cho, S.; Chae, H.-D.; Zhou, W.; Zhang, L.; Khanna, A.; Zeng, X.; Du, X.; Zhu, H.; Chang, T.-P.; Max, N.; Kumar, M.; Chen, C.; Lee, L. Strategic Use of Benzylic Alcohols Reveals Cryptic Hydrogen-Bonding Interactions: Discovery of HBC-12551 as a Potent Noncovalent Bruton's Tyrosine Kinase Inhibitor. *J. Med. Chem.* **2026**, *69* (3), 2867–2887. https://doi.org/10.1021/acs.jmedchem.5c02785

10b.1.11



Chen, L.; Liao, G.; Liu, B. Ligand-Enabled Nickel(II)-Catalyzed β-C(sp^3^)–H Thiolation of Ketones. *Org. Lett*. **2024**, *26* (42), 9103–9107. https://doi.org/10.1021/acs.orglett.4c03404

10b.1.12



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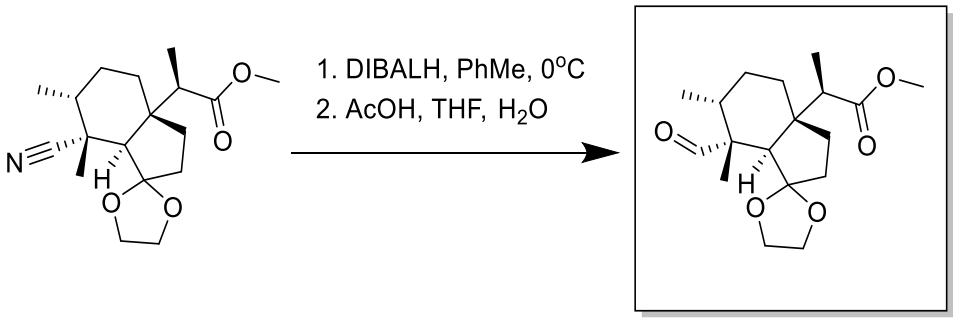
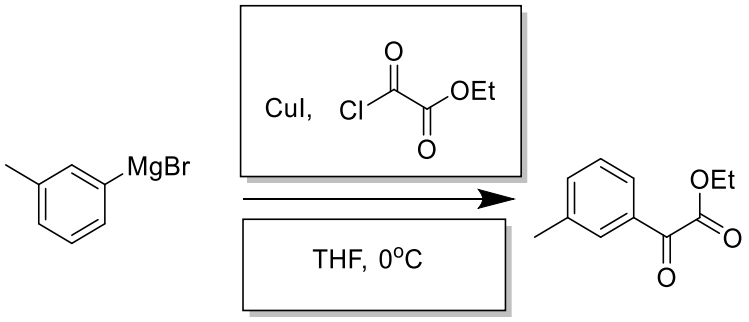
10b.1.13



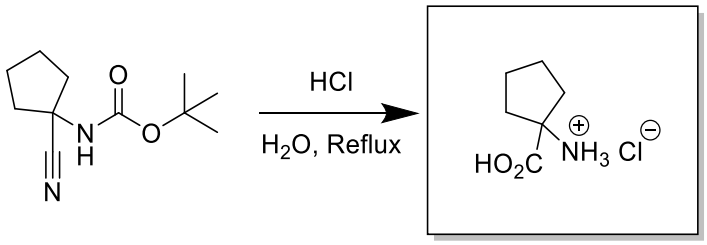
Goethe, O.; DiBello, M.; Herzon, S. B. Total Synthesis of Structurally Diverse Pleuromutilin Antibiotics. *Nat. Chem.* **2022**, *14* (11), 1270-1277. https://doi.org/10.1038/s41557-022-01027-7

10b.1.14



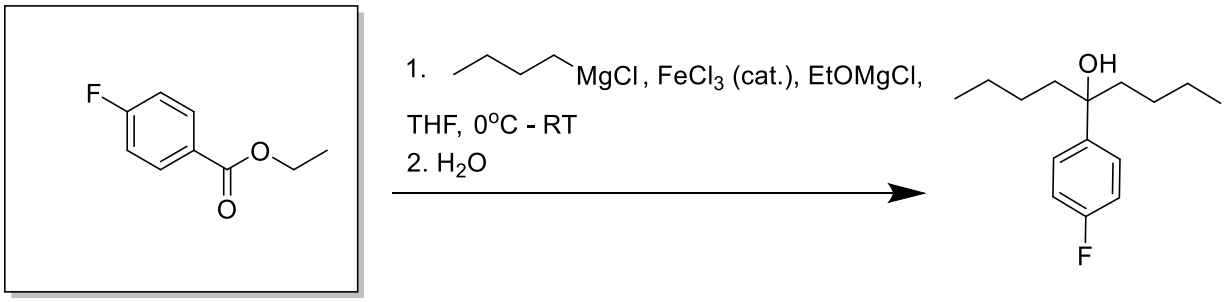
Yang, Y.-C.; Li, W.-S.; Uang, T.-Y.; Kuo, T.-S.; Wu, H.-L. Access to Chiral Tertiary α-Hydroxyesters via Rhodium-Catalyzed Enantioselective Allylation of α-Ketoesters. *Chem. Asian J.* **2026**, *21* (2), e70585. https://doi.org/10.1002/asia.70585

10b.1.15



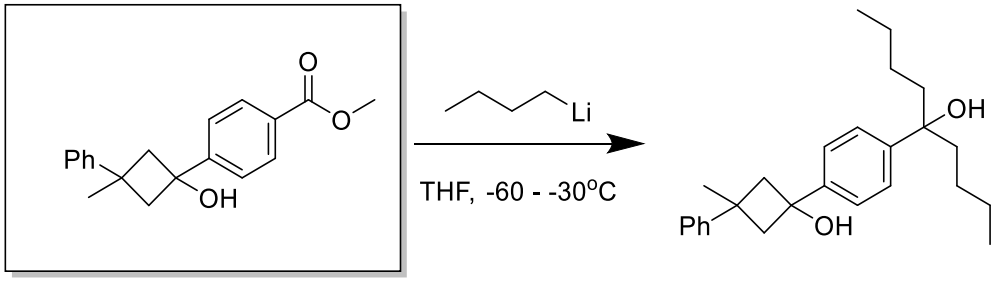
Zhang, Y.-H.; Jiao, F.-N.; Cao, F.-Y.; Zhao, M.-Z.; Sun, B.-Y.; Zhou, M.-J.; Xiao, H.; Dai, J.-J. Practical and Direct Synthesis of α-Aminonitriles Using N-Boc-O-tosyl Alkylhydroxylamines and TMSCN. *Chem. Commun*. **2026**, *62* (66), 16531–16535. https://doi.org/10.1039/D6CC03609K

10b.1.16



Cahiez, G.; Lefèvre, G.; Moyeux, A.; Guerret, O.; Gayon, E.; Guillonneau, L.; Lefèvre, N.; Gu, Q.; Zhou, E. Gram-Scale, Cheap, and Eco-Friendly Iron-Catalyzed Cross-Coupling between Alkyl Grignard Reagents and Alkenyl or Aryl Halides. *Org. Lett*. **2019**, *21* (8), 2679–2683. https://doi.org/10.1021/acs.orglett.9b00665

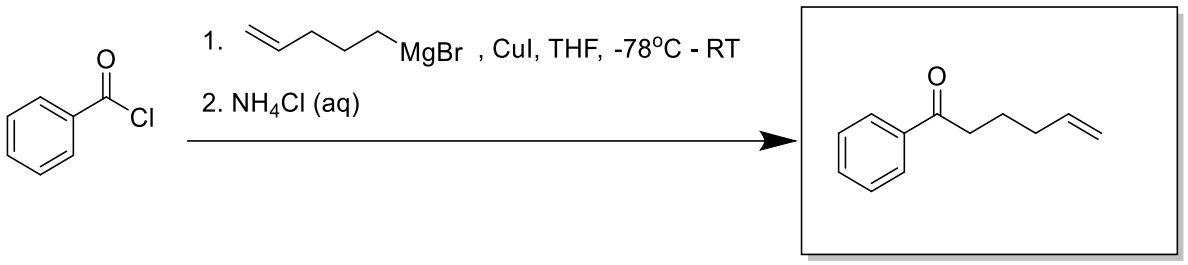
10b.1.17



Note: The authors used butyl lithium instead of a Grignard reagent.

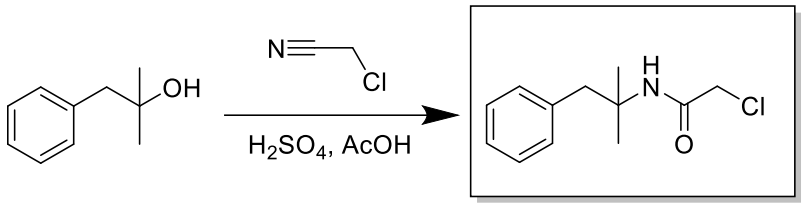
Parra-García, S.; Ballester-Ibáñez, M.; García-López, J.-A. Pd-Catalyzed Formal [2 + 2]-Retrocyclization of Cyclobutanols via 2-Fold Csp^3^–Csp^3^ Bond Cleavage. *J. Org. Chem*. **2024**, *89* (2), 882–886. https://doi.org/10.1021/acs.joc.3c01750

10b.1.18



Wang, Y.; Hong, F.; Robertson, C. M.; Mudd, R. J.; Bower, J. F. Iridium-Catalyzed Stereoselective α-Alkylation of α-Hydroxy Ketones with Minimally Polarized Alkenes. *J. Am. Chem. Soc*. **2026**, *148* (4), 3911–3917. https://doi.org/10.1021/jacs.5c19724

10b.1.19

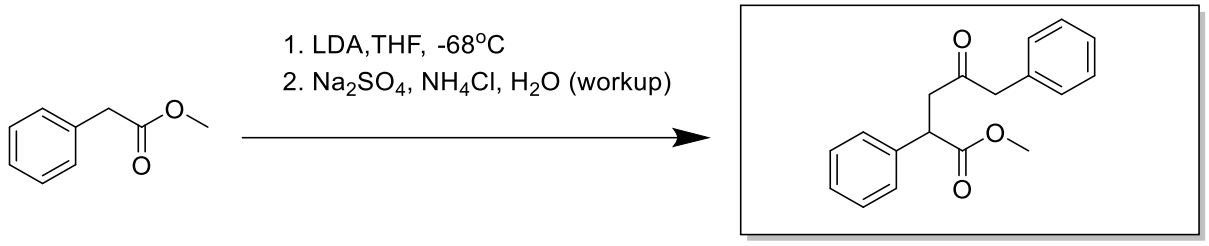


Enudi, O. C.; Twitty, J. C.; Rotella, M. E.; Underwood, S. J.; Kozlowski, M. C.; Watson, M. P. Pyridinium Design for Deaminative Reactions of Sterically Encumbered Alkyl Amines. *Org. Lett*. **2026**, *28* (22), 7009–7014. https://doi.org/10.1021/acs.orglett.6c01717

Section 11a – Box-Type Questions

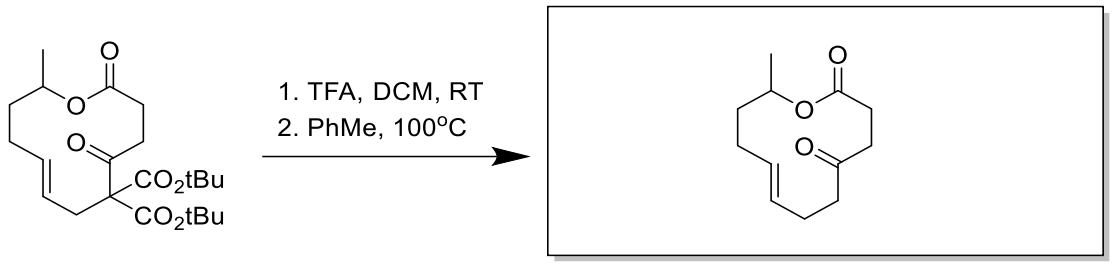
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

11a.1.1



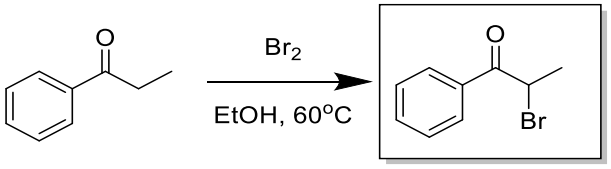
Tang, W.; Guo, L.; Yang, L.; Qiu, L.; Liu, H.; Yang, M. Enhanced Utilization of Ester Enolates in Slow-Kinetic α-Functionalization of Esters: Insights into Enolate Consumption and Preservation Strategies. *Chem. Eng. Sci.* **2026**, *327*, 123675. https://doi.org/10.1016/j.ces.2026.123675

11a.1.2



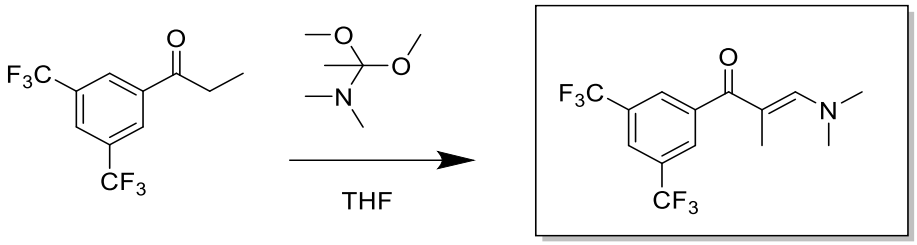
Yang, X.-H.; Jie, T.-C.; Lu, Y.-P.; Chen, S.-Q.; Ran, G.-Y. Combining Palladium and Metal Alkoxide Enables Chemoselective Access to Flexible Allyl-Pd Oxa-dipoles for Higher-Order Cycloadditions. *Org. Lett.* **2026**, *28* (4), 1247-1252. https://doi.org/10.1021/acs.orglett.5c05011

11a.1.3



Özkan, G.; Biçer, A.; Bulca, Z. T.; Kurt, E.; Akbulut, D.; Köse, F. A. Synthesis, Structural Characterization, and Structure-Activity Relationship of Thiazole Derivatives: A Combined Experimental and Computational Study. *J. Mol. Struct.* **2026**, *1374*, 146832. https://doi.org/10.1016/j.molstruc.2026.146832

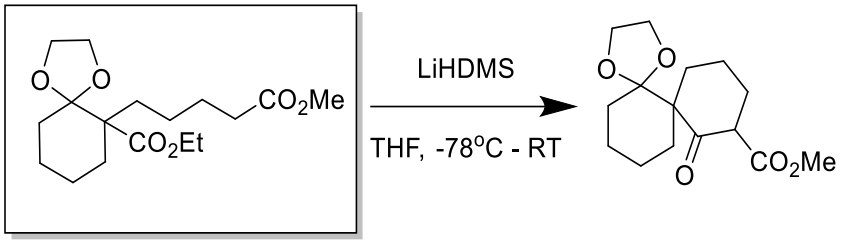
11a.1.4



Note: Assume there is some acid present in the reaction.

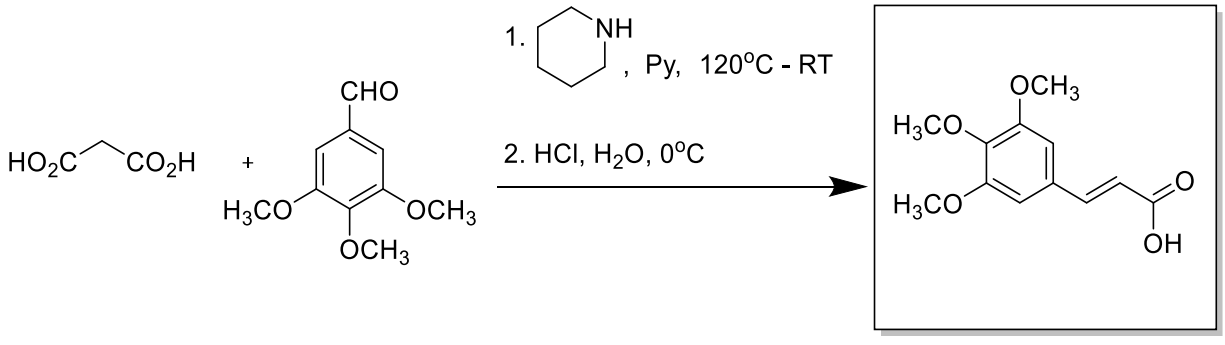
Miao, H.; Qin, Y.; Shao, D.; Chen, Q.; Pan, Y.; Lei, M.; Wu, R.; Ye, X.; Wang, X.; Zhu, Y. Discovery of SZJK-0421: A Novel Potent, Low Toxicity, Selective Second Generation of CRM1 Inhibitor for the Treatment of Both Hematological and Solid Tumors. *J. Med. Chem.* **2024**, *67* (22), 20595–20618. https://doi.org/10.1021/acs.jmedchem.4c02169

11a.1.5



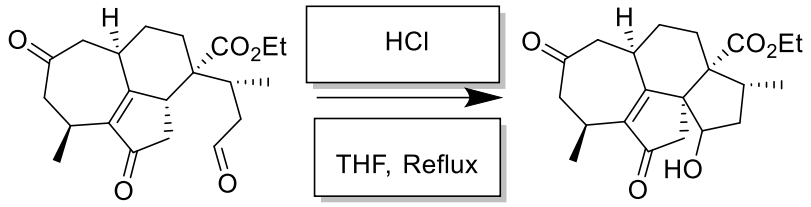
Broeker, J.; Waterson, A. G.; Hodges, T. R.; Abbott, J. R.; Arnold, A.; Böttcher, J.; Braun, N.; Cui, J.; Fuchs, J. E.; Gerstberger, T.; Gogg, S.; Hanner, S.; Herdeis, L.; Howell, L. W.; Mantoulidis, A.; Mayer, M.; Phan, J.; Rocchetti, F.; Sankar, K. Discovery of BI-2493, a Pan-KRAS Inhibitor Showing In Vivo Efficacy. *J. Med. Chem.* **2025**, *68* (15), 15649-15668. https://doi.org/10.1021/acs.jmedchem.5c00576

11a.1.6



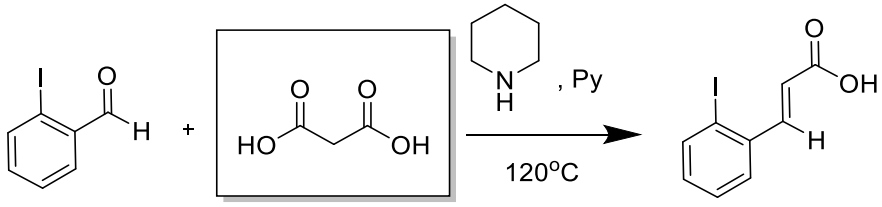
Shi, S.; Tu, J.; Zhong, M.; Xi, J.; Hao, J.; Wu, Z.; Zhang, H.; Bai, Z.; Zhang, B. Structure-Guided Optimization of PAO-PDT Yields TrxR Inhibitors as Potential Anticancer Agent. *Eur. J. Med. Chem.* **2026**, *303*, 118407. https://doi.org/10.1016/j.ejmech.2025.118407

11a.1.7



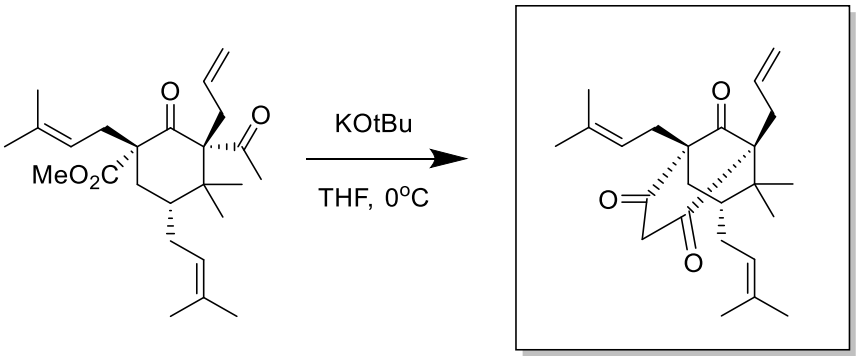
Mao, H.-K.; Wang, Q.; Xu, J. Enantioselective Total Synthesis of Fortalpinoid Q via a TEMPO^{+} BF_4^{-} -Mediated Dehydrative Nazarov Cyclization. *J. Am. Chem. Soc.* **2025**, *147* (11), 9079–9084. https://doi.org/10.1021/jacs.5c00319

11a.1.8



Liu, S.; Díaz-Fernández, M.; Zhang, M.; Huang, F.; Chen, Y.; Yang, Y.; Marín-Beloqui, J. M.; Lan, J.; You, J.; Casado, J.; Zhang, C. Azuperylene: The Nonalternant Isomer of Perylene. *Angew. Chem. Int. Ed.* **2025**, *64* (29), e202505897. https://doi.org/10.1002/anie.202505897

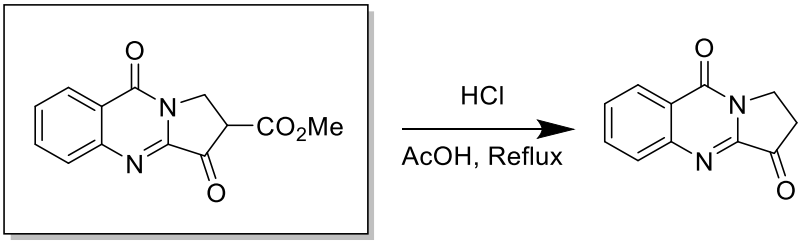
11a.1.9



Hint: A new ring is formed in the product.

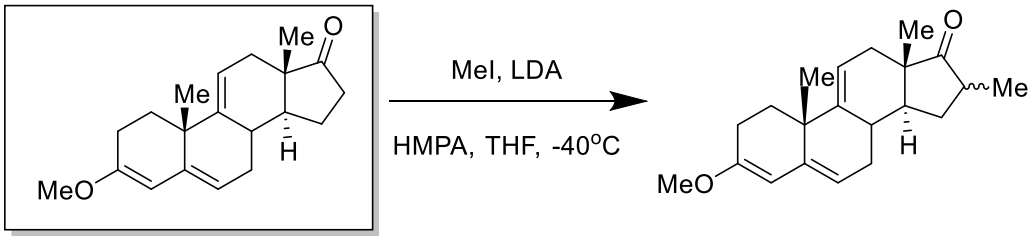
Wan, Y.; Wu, H.; Xia, L.; Liu, S.; Ren, Y.; Xu, H.; Zheng, C. Sequential Dieckmann Cyclization Enables the Total Synthesis of 7- *Epi* -Clusianone and 18-Hydroxy-7- *Epi* -Clusianone. *Org. Biomol. Chem.* **2024**, *22* (3), 529–537. https://doi.org/10.1039/D3OB01840G

11a.1.10



D'Almeida, R. E.; Chen, P.; Huang, Y.; Goetz, E.; Sammeta, V. R.; Yang, B.; Rao, R. P.; Rasapalli, S.; Elfawal, M. A. Design, Synthesis, and Biological Evaluation of a Focused Pyrrolo- and Pyrido-Quinazolinone Natural Products-Templated Library for Anti-Fungal and Anthelmintic Activities. *Bioorg. Med. Chem.* **2026**, *134*, 118517. https://doi.org/10.1016/j.bmc.2025.118517

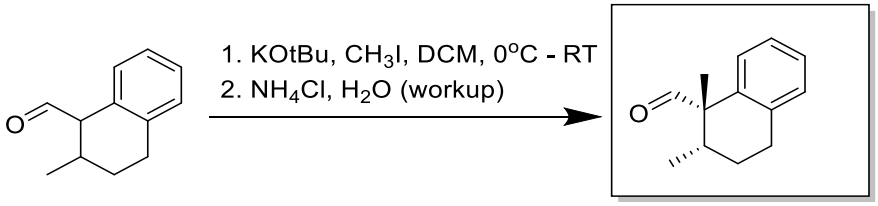
11a.1.11



Assume there is only one equivalent of MeI added.

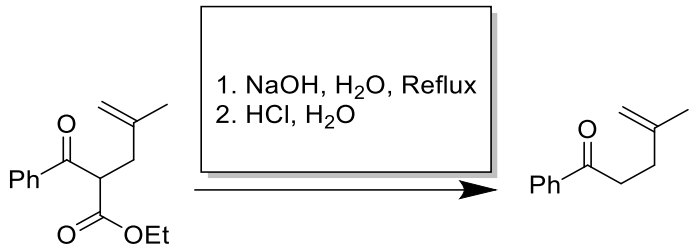
Wei, J.; Zhang, Y.; Liu, M.; Ning, Y.; Cao, Y.; Chen, F.-E. Divergent Chemo- and Biocatalytic Route to 16β-Methylcorticoids: Asymmetric Synthesis of Betamethasone Dipropionate, Clobetasol Propionate, and Beclomethasone Dipropionate. *Angew. Chem. Int. Ed.* **2024**, *63* (4), e202313952. https://doi.org/10.1002/anie.202313952

11a.1.12



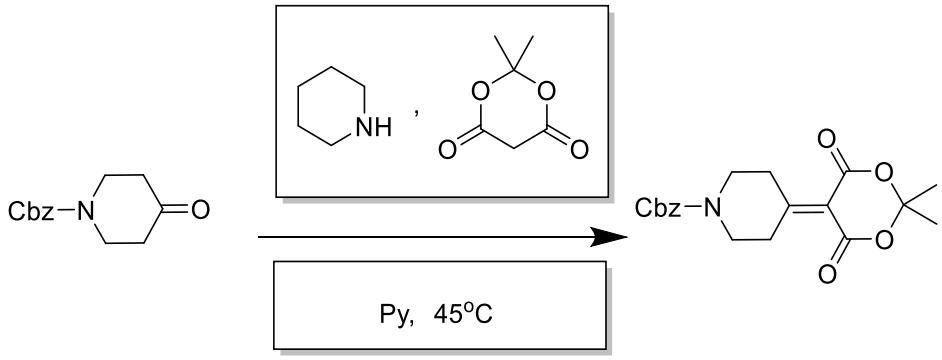
Kong, L.; Gan, X.-C.; van der Puyl Lovett, V. A.; Shenvi, R. A. Alkene Hydrobenzylation by a Single Catalyst That Mediates Iterative Outer-Sphere Steps. *J. Am. Chem. Soc.* **2024**, *146* (4), 2351-2357. https://doi.org/10.1021/jacs.3c13398

11a.1.13



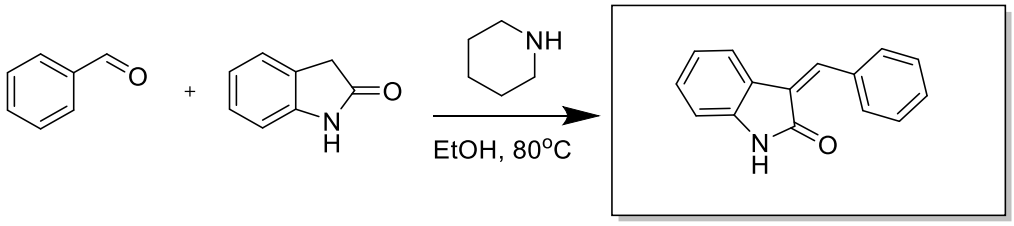
Chen, T.; Li, J.; Hu, X.; Li, J.; Wang, Z.; Yan, Z.; Xu, Z.-F.; Yu, M.; Li, C.-Y. Oxidative Cleavage of Olefins via *N*-Arylaminophthalimide-Derived Aryl Radicals under Air. *Org. Lett.* **2026**, *28* (18), 5734-5739. https://doi.org/10.1021/acs.orglett.6c01182

11a.1.14



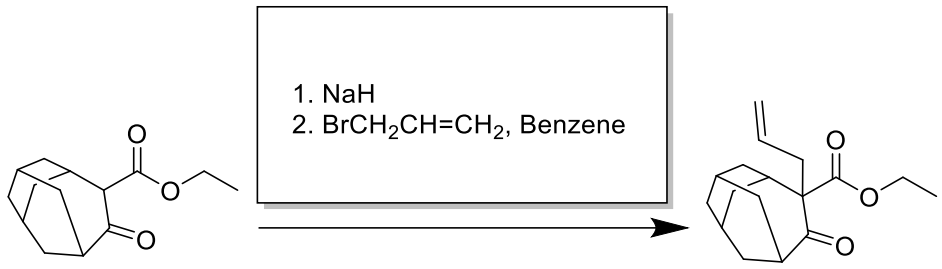
Chu, G.-H.; Le Bourdonnec, B.; Gu, M.; Saeui, C. T.; Dolle, R. E. General and Efficient Synthetic Approach to Novel Tricyclic Spiroketones. *Tetrahedron* **2009**, *65* (27), 5161-5167. https://doi.org/10.1016/j.tet.2009.04.094

11a.1.15



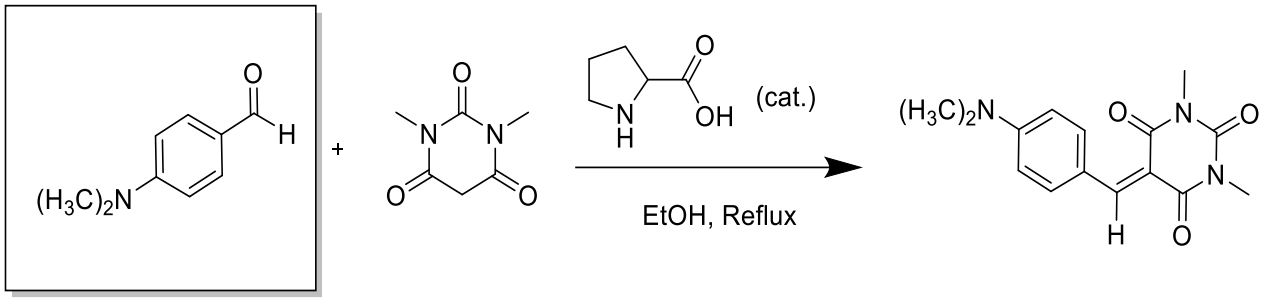
Banyangala, M.; K. S., S.; Thushara, R.; C. S., A.; K., L. V.; Suresh, C. H.; Purushothaman, J.; Somappa, S. B. Regioselective House-Meinwald Rearrangement in Oxindoles: Access to Substituted Quinolinones. *Org. Biomol. Chem.* **2026**, *24* (10), 2028-2033. https://doi.org/10.1039/D6OB00128A

11a.1.16



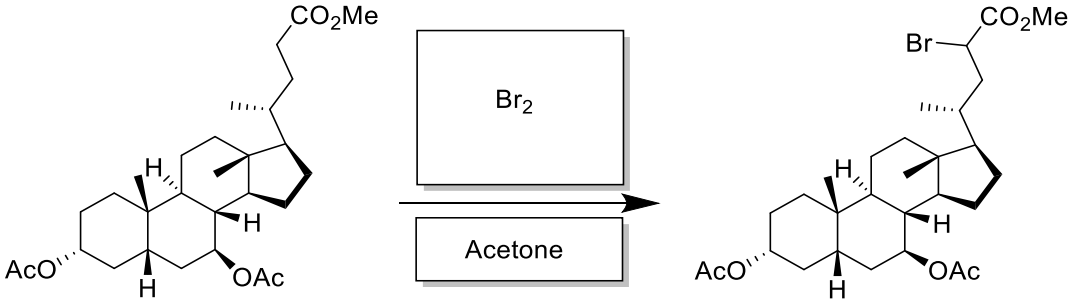
Tkachenko, I. M.; Mankova, P. A.; Rybakov, V. B.; Golovin, E. V.; Klimochkin, Y. N. Wagner–Meerwein Type Rearrangement in 5-Oxohomoadamantane Series. *Org. Biomol. Chem.* **2020**, *18* (3), 465–478. https://doi.org/10.1039/C9OB02060H.

11a.1.17



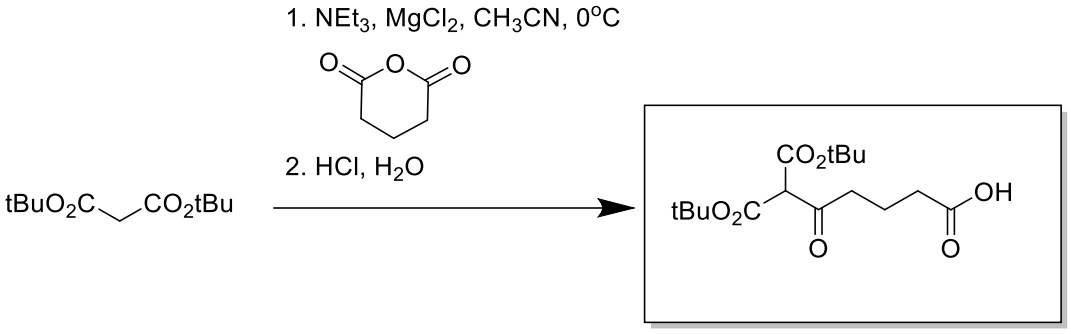
Li, P.; Zhang, J.; Wang, Z.; Li, C.; Wu, H.; Lei, M.; Yan, G.; Tian, H.; Gu, R.; Qu, D.-H. Catalyst-Free Dynamic Covalent Knoevenagel/Hydrazide Condensation for Polyacylhydrazones and Covalent Adaptable Networks. *Angew. Chem. Int. Ed.* **2025**, *64* (29), e202506939. https://doi.org/10.1002/anie.202506939

11a.1.18



Yang, R.; Du, C.; Cao, T.; Wang, G.; Jiang, X.; Gao, J.; Lin, T.; Sun, C.; Ding, R.; Tian, W.; Chen, H. Synthesis and Anti-Hepatoma Activities of U12 Derivatives Arresting G0/G1 Phase and Inducing Apoptosis by PI3K/AKT/mTOR Pathway. *Pharmaceuticals* **2022**, *15* (1), 107. https://doi.org/10.3390/ph15010107

11a.1.19



Yang, X.-H.; Jie, T.-C.; Lu, Y.-P.; Chen, S.-Q.; Ran, G.-Y. Combining Palladium and Metal Alkoxide Enables Chemoselective Access to Flexible Allyl-Pd Oxa-Dipoles for Higher-Order Cycloadditions. *Org. Lett.* **2026**, *28* (4), 1247–1252. https://doi.org/10.1021/acs.orglett.5c05011

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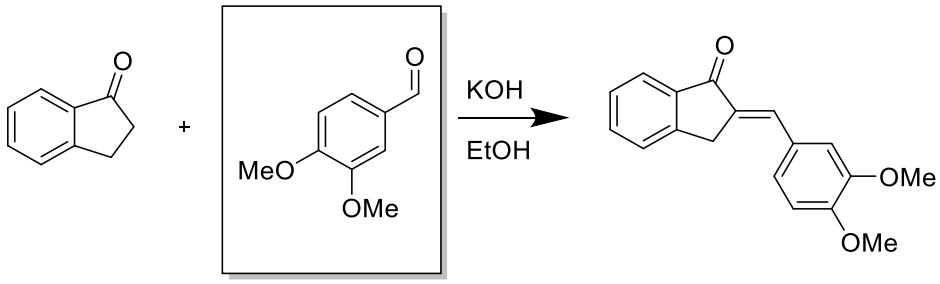
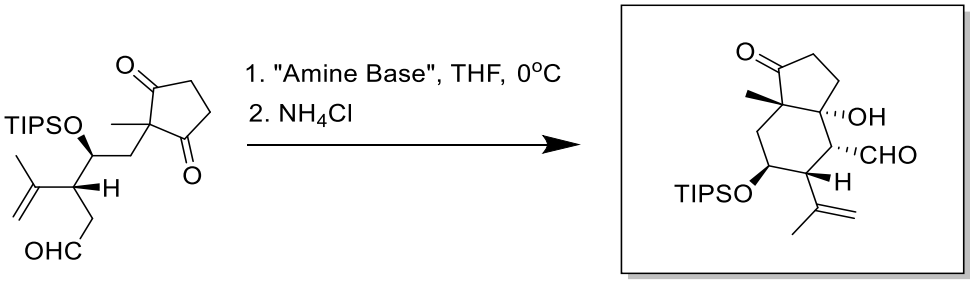


Story, J. B.; Ringler, K. E.; Nguyen, C. L.; Drance, M. J.; Howard, E. M. Synthesis of 2-Naphthols via a Trifluoroacetic Acid-Mediated Epoxy Alcohol Rearrangement. *J. Org. Chem.* **2026**, *91* (14), 5249–5254. https://doi.org/10.1021/acs.joc.6c00021

11a.1.21



Note: The article employs a specialized amine base to facilitate the transformation and achieve the desired stereochemical outcome.

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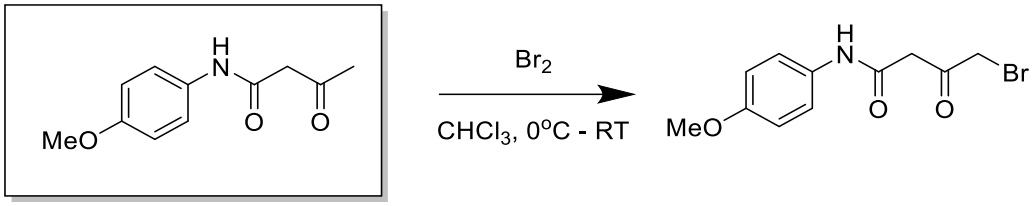
11a.1.22



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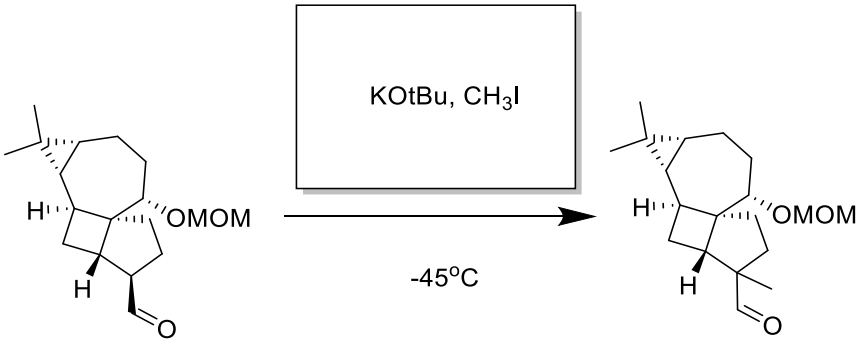
11a.1.23



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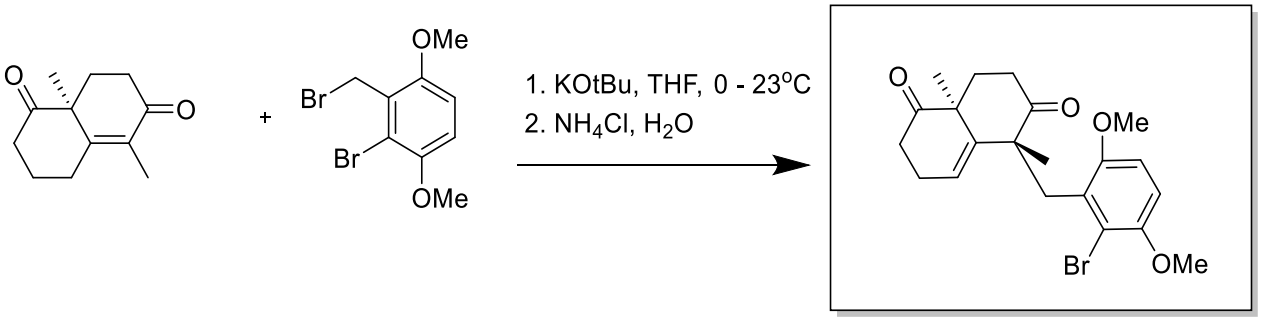
11a.1.24



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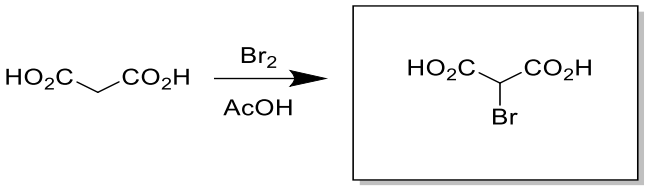
11a.1.25



Hassan, H. A.; Abdel-Aziz, M.; Abuo-Rahma, G. E.-D. A. A.; Farag, H. H. 1-Malonyl-1,4-dihydropyridine as a Novel Carrier for Specific Delivery of Drugs to the Brain. *Bioorg. Med. Chem.* **2009**, *17* (4), 1681-1692. https://doi.org/10.1016/j.bmc.2008.12.051

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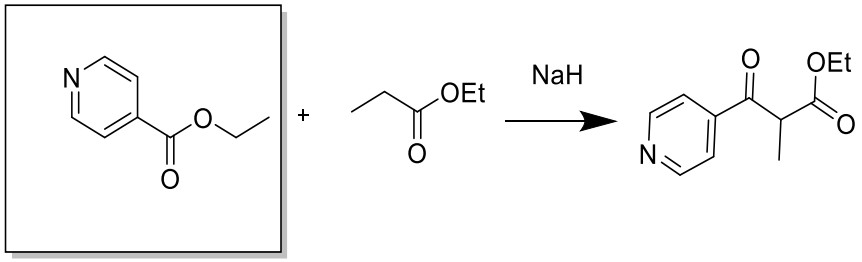

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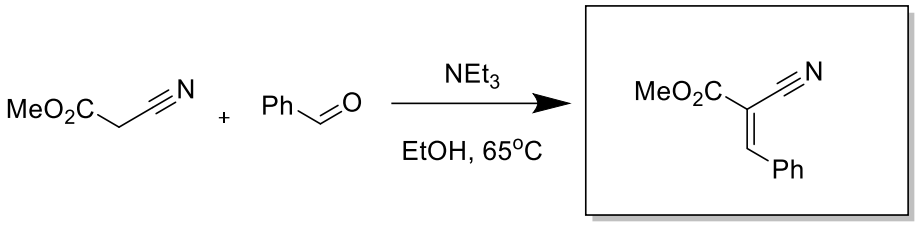

Narayanan, D.; Tran, K. T.; Pallesen, J. S.; Solbak, S. M. Ø.; Qin, Y.; Mukminova, E.; Luchini, M.; Vasilyeva, K. O.; González Chichón, D.; Goutsiou, G.; Poulsen, C.; Haapanen, N.; Popowicz, G. M.; Sattler, M.; Olagnier, D.; Gajhede, M.; Bach, A. Development of Noncovalent Small-Molecule Keap1-Nrf2 Inhibitors by Fragment-Based Drug Discovery. *J. Med. Chem.* **2022**, *65* (21), 14481–14526. https://doi.org/10.1021/acs.jmedchem.2c00830

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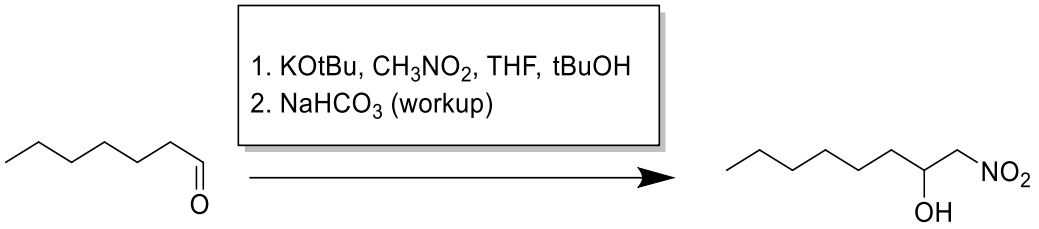

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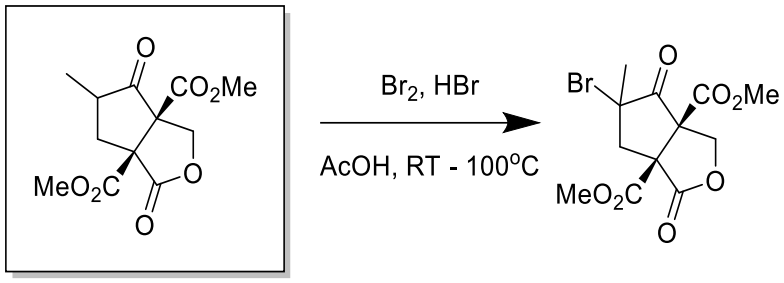
11a.1.29



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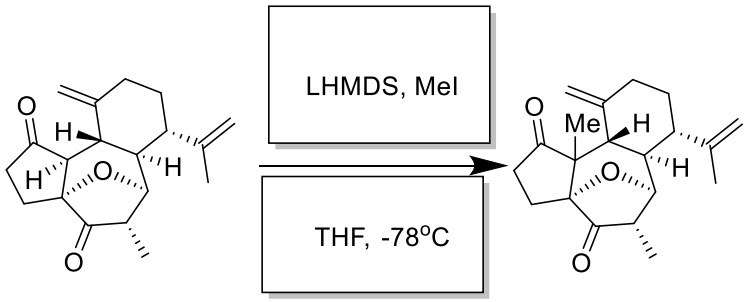

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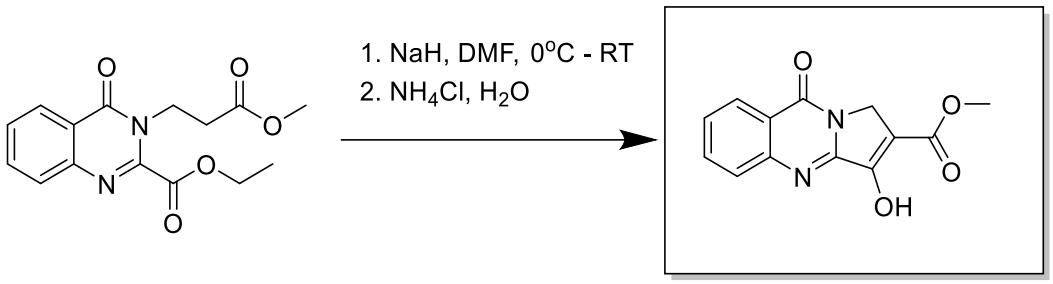

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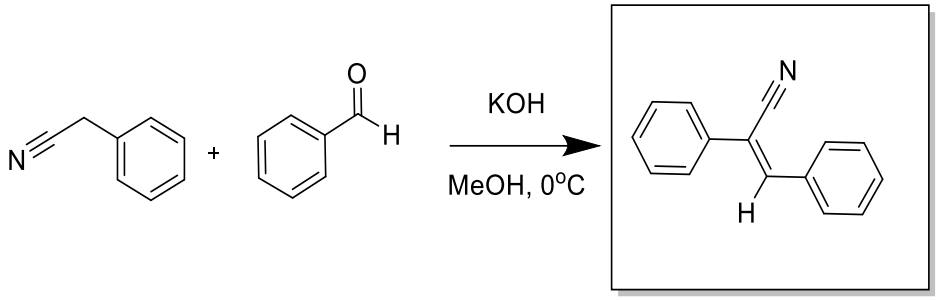

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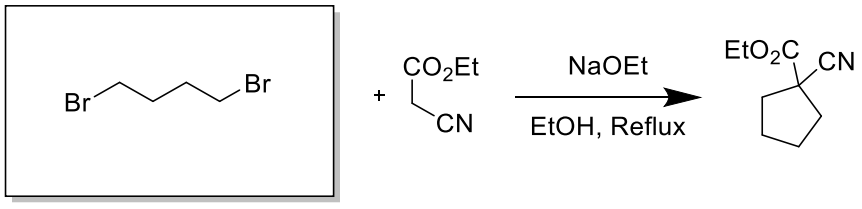

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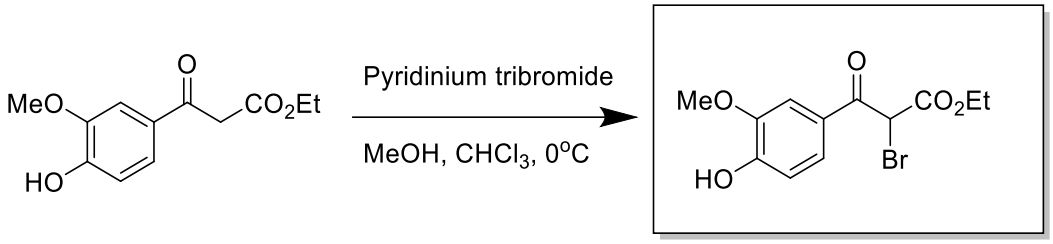
11a.1.34



Note: Pyridinium tribromide is a source for molecular bromine.

Bourmaud, C. L.; Bertella, S.; Bosch Rico, A.; Karlen, S. D.; Ralph, J.; Luterbacher, J. S. Quantification of Native Lignin Structural Features with Gel-Phase 2D-HSQC$_0$ Reveals Lignin Structural Changes During Extraction. *Angew. Chem. Int. Ed.* **2024**, *63* (31), e202404442. https://doi.org/10.1002/anie.202404442

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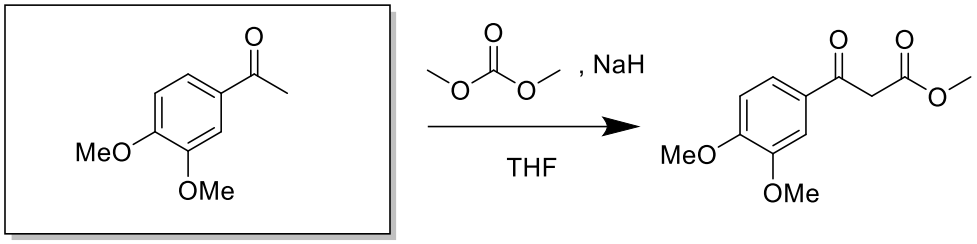

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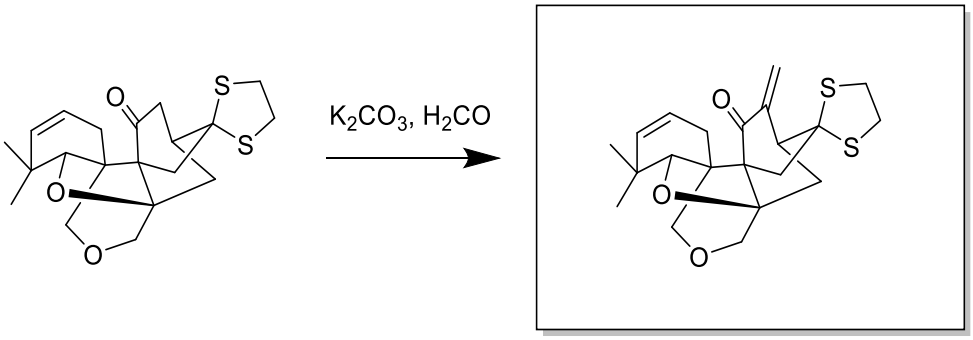
11a.1.36



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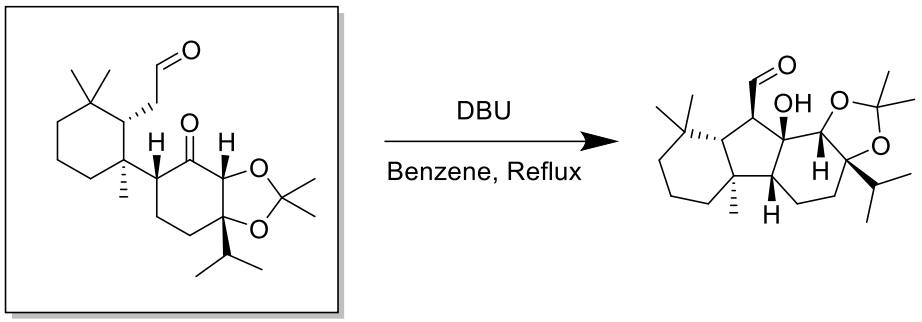

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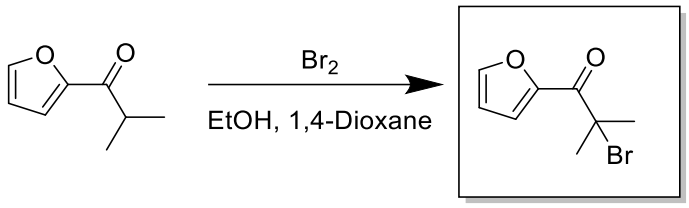
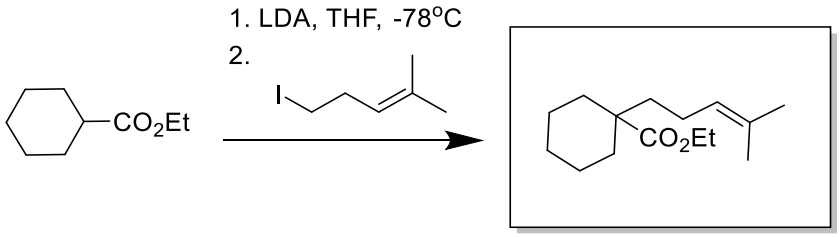
11a.1.38



Seleznev, Y. A.; Lavrinchenko, I. A.; Moseev, T. D.; Varaksin, M. V.; Tsmokaluk, A. N.; Mazhukin, D. G.; Tikhonov, A. Y.; Charushin, V. N.; Chupakhin, O. C(2) and C(5) Nucleophilic Functionalization of 4 *H* -Imidazole-3-Oxide Exposed to Carboranyllithium. *J. Org. Chem.* **2025**, *90* (50), 17688–17704. https://doi.org/10.1021/acs.joc.5c01956

11a.1.39



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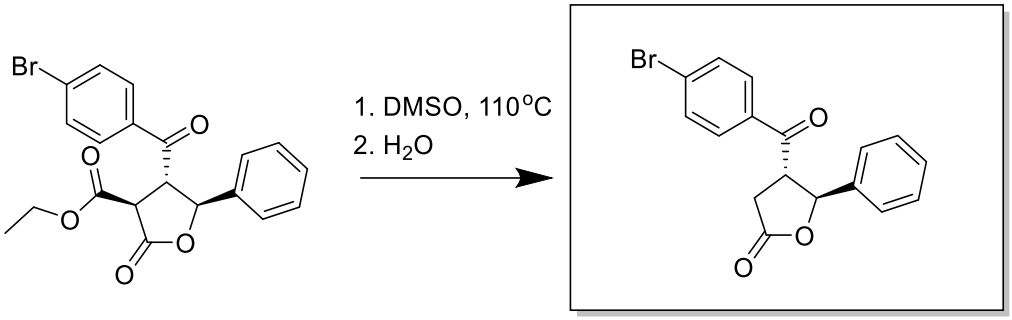
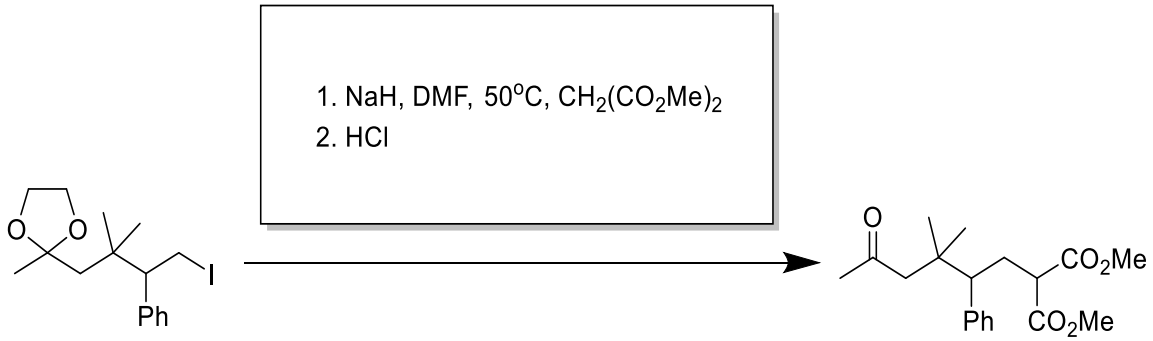
11a.1.40



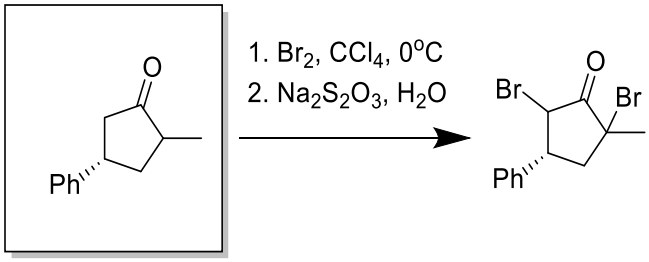
Deerkadharshini, M.; Ezhilgnanadevi, E.; Srinivasan, K. Stereoselective Synthesis of 2-(β-Aroylstyryl)malonates and γ-Butyrolactones through Lewis Acid-Mediated Ring-Opening Reactions of Aroyl-Substituted Donor-Acceptor Cyclopropanes. *J. Org. Chem.* **2026**, *91* (27), 9243-9251. https://doi.org/10.1021/acs.joc.6c00070

11a.1.41



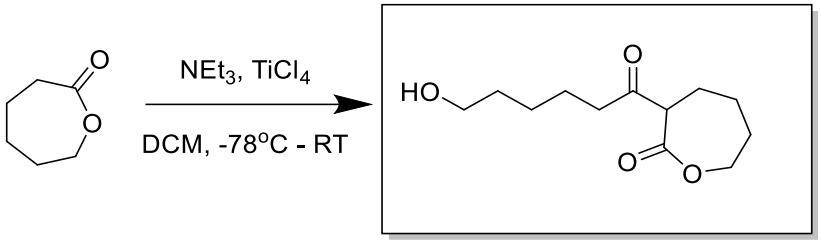
Wan, Y.; Wu, H.; Xia, L.; Liu, S.; Ren, Y.; Xu, H.; Zheng, C. Sequential Dieckmann Cyclization Enables the Total Synthesis of 7- *Epi* -Clusianone and 18-Hydroxy-7- *Epi* -Clusianone. *Org. Biomol. Chem.* **2024**, *22* (3), 529–537. https://doi.org/10.1039/D3OB01840G

11a.1.42



Saha, D.; Wu, J. Selectivity Rules for the Dearomative (3+2) Annulation Reaction Between Substituted Indoles and Oxyallyl Cations. *Adv. Synth. Catal.* **2025**, *367* (7), e202401536. https://doi.org/10.1002/adsc.202401536

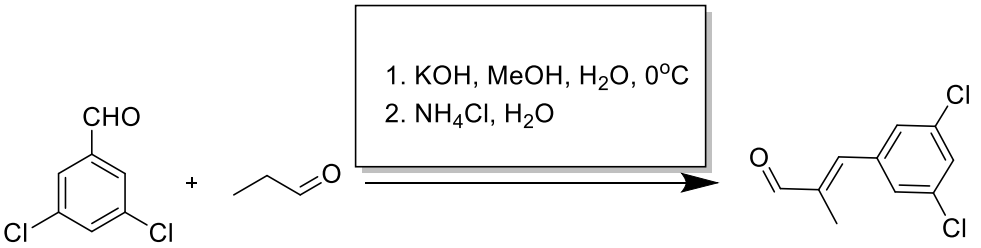
11a.1.43



Note: $TiCl_4$ is a Lewis Acid used to make a carbonyl group more reactive to nucleophilic attack.

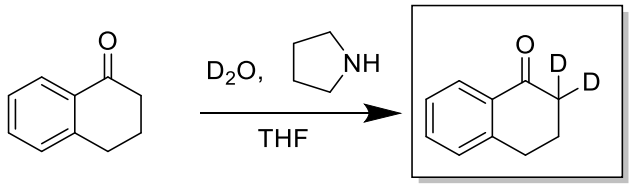
Nabi, A.; Atmuri, N. D. P.; Arnold, D.; Saadati, F.; Tran, H.; Adak, T.; Dake, G. R.; Ciufolini, M. A. Claisen Self-Condensation of Lactones in the Synthesis of Ionizable Lipids. *J. Org. Chem.* **2024**, *89* (17), 12775–12778. https://doi.org/10.1021/acs.joc.4c01193

11a.1.44



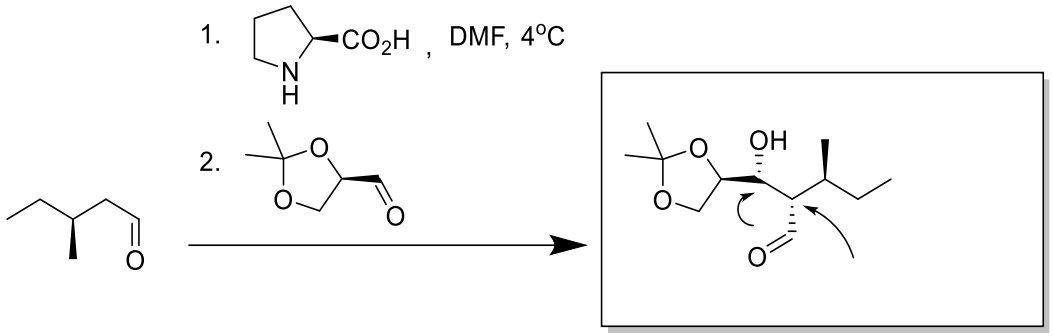
Zeng, Q.-Y.; Zhang, Y.-Q.; Cheng, X.-Y.; Xu, H.; Dai, H.-X. Synthesis of Polysubstituted Pyrroles via (2 + 2 + 1) Cyclization of Enone Oxime Ethers with Alkynes and Diaziridinone. *J. Org. Chem.* **2026**, *91* (3), 1271–1275. https://doi.org/10.1021/acs.joc.5c01879

11a.1.45



Ikonnikova, V. A.; Solyev, P. N.; Al Mufti, A. M.; Kungurtsev, K. D.; Korlyukov, A. A.; Baranov, M. S.; Mikhaylov, A. A. Synthesis of Chroman Derivatives by Group Transposition and Atom Swapping in 1-Tetralones: Single-Atom Editing Enabled by Oxidative Ring Contraction of Benzoxepine Silyl Ketene Acetals. *Angew. Chem. Int. Ed.* **2025**, *64* (31), e202506564. https://doi.org/10.1002/anie.202506564

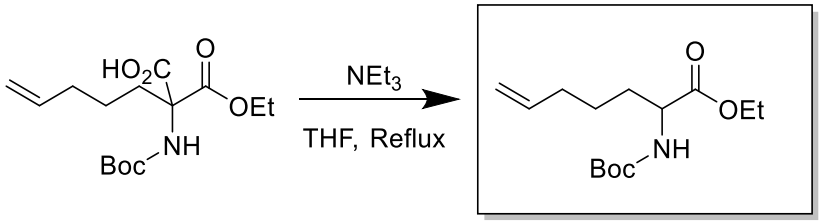
11a.1.46



For introductory organic chemistry courses, learners do not have to worry about the arrangement of the stereocenters indicated.

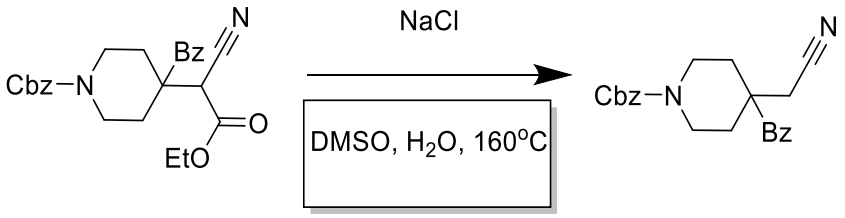
Kumaraswamy, G.; Markondaiah, B. Stereoselective Synthesis of Belactosin C and Its Derivatives Using a Catalytic Proline Catalyzed Crossed-Aldol Reaction. *Tetrahedron Lett.* **2007**, *48* (10), 1707–1709. https://doi.org/10.1016/j.tetlet.2007.01.059

11a.1.47



Villela, L. F.; Stoerkler, T.; Labbé, L.; Barriault, L. Bismuth-Catalyzed Photoinduced Ligand-to-Metal Charge Transfer (LMCT) Hydrodecarbonylation of Aldehydes. *Org. Lett.* **2026**, *28* (9), 3057-3062. https://doi.org/10.1021/acs.orglett.6c00395

11a.1.48



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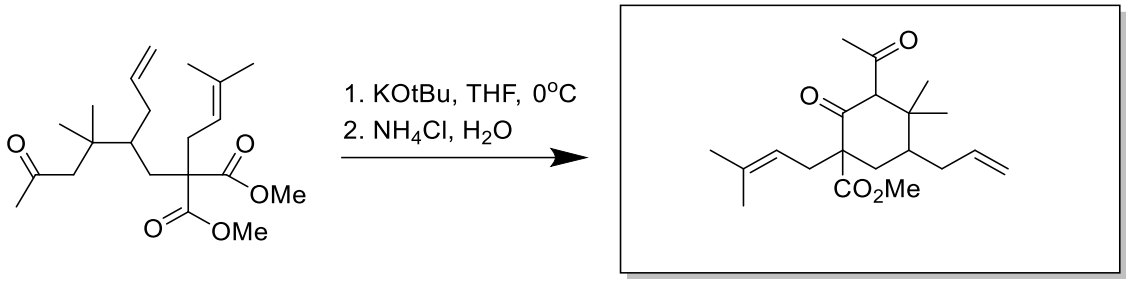
Section 11b – Box-Type Questions

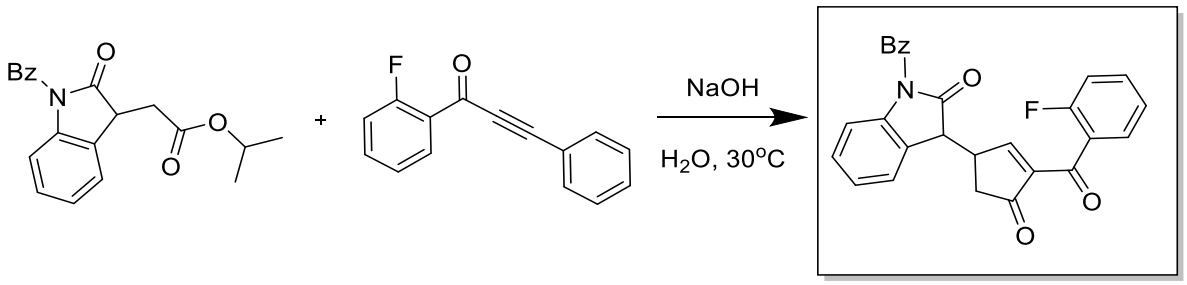
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

11b.1.1



Wan, Y.; Wu, H.; Xia, L.; Liu, S.; Ren, Y.; Xu, H.; Zheng, C. Sequential Dieckmann Cyclization Enables the Total Synthesis of 7- *Epi* -Clusianone and 18-Hydroxy-7- *Epi* -Clusianone. *Org. Biomol. Chem.* **2024**, *22* (3), 529–537. https://doi.org/10.1039/D3OB01840G

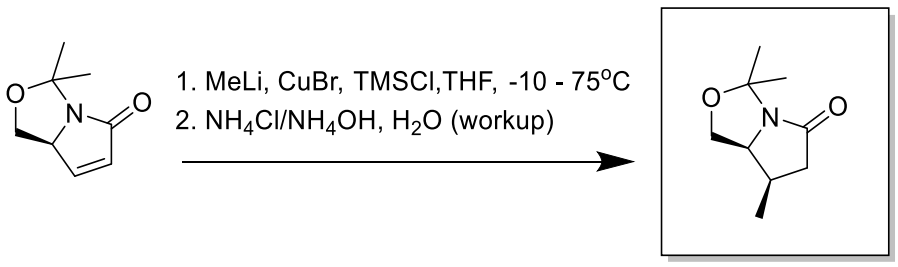
11b.1.2



Hint: A five-membered ring is formed.

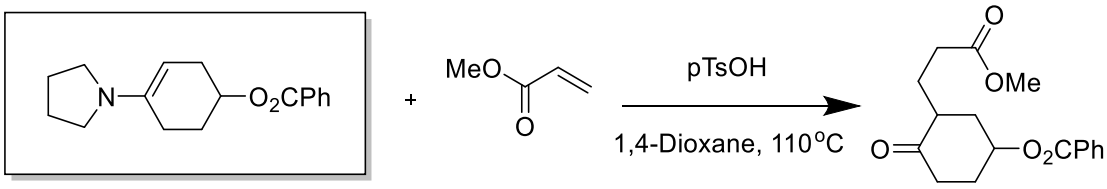
Lang, J.; Li, Y.; Kang, T.; Feng, X.; Liu, X. Organocatalytic Asymmetric Michael/Dieckmann Cyclization Reaction of Alkynones To Construct Spirocyclopentene Oxindoles. *Org. Lett.* **2019**, *21* (17), 6897–6902. https://doi.org/10.1021/acs.orglett.9b02519

11b.1.3



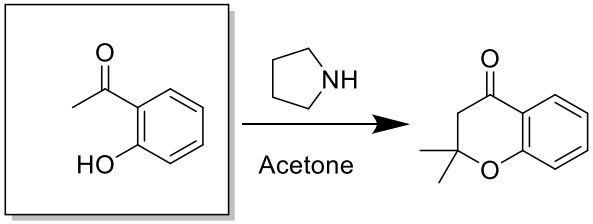
Wright, S. W.; Choi, C.; Chung, S.; Boscoe, B. P.; Drozda, S. E.; Mousseau, J. J.; Trzupek, J. D. Reversal of Diastereoselection in the Conjugate Addition of Cuprates to Unsaturated Lactams. *Org. Lett.* **2015***, 17* (21), 5204–5207. https://doi.org/10.1021/acs.orglett.5b02533

11b.1.4



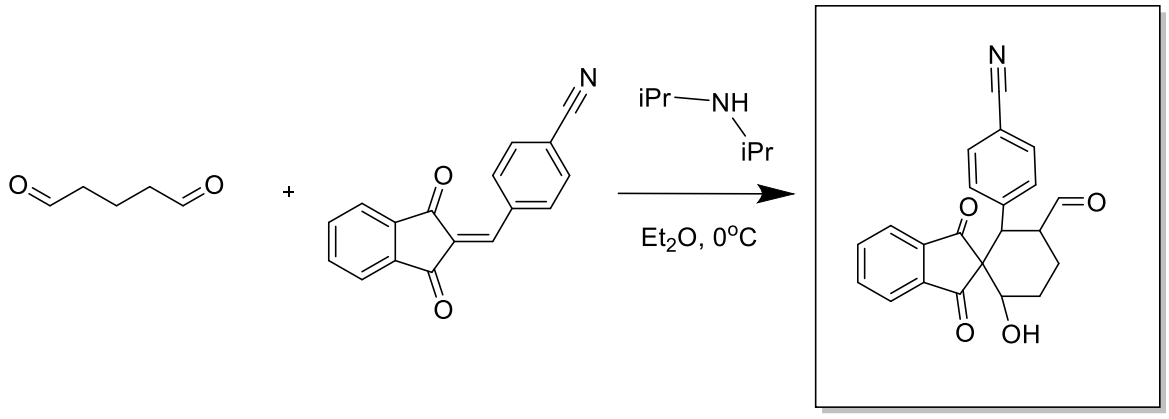
Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in *sp*^{3}-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

11b.1.5



Dubrovskiy, A. V.; Larock, R. C. Intermolecular C-O Addition of Carboxylic Acids to Arynes. *Org. Lett.* **2010**, *12* (14), 3117-3119. https://doi.org/10.1021/ol101017z

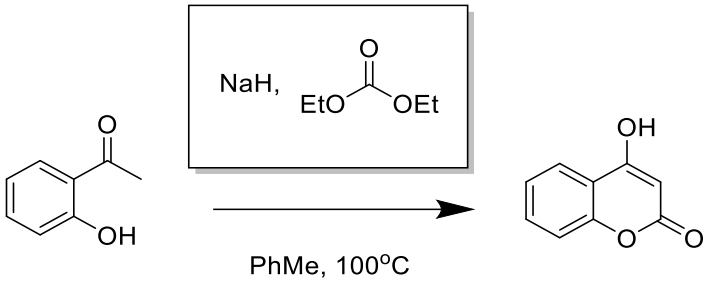
11b.1.6



Note: The authors used a chiral amine catalyst (absent from the reaction above to simplify the reaction) to achieve the desired stereochemistry of the product.

Anwar, S.; Li, S. M.; Chen, K. Organocatalytic Synthesis of Substituted Spirocyclohexane Carbaldehydes via [4 + 2] Annulation Strategy between 2-Arylideneindane-1,3-Diones and Glutaraldehyde. *Org. Lett.* **2014**, *16* (11), 2993–2995. https://doi.org/10.1021/ol501160k

11b.1.7



Aarjane, M.; Slassi, S.; Ait Mouha, M.; El-Ghayoury, A.; Yamni, K.; Amine, A. A New Coumarin Derivative: Synthesis, Crystal Structure, Computational Studies, and Dual Antioxidant–Antibacterial Activity. *J. Mol. Struct.* **2026**, *1349*, 143839. https://doi.org/10.1016/j.molstruc.2025.143839

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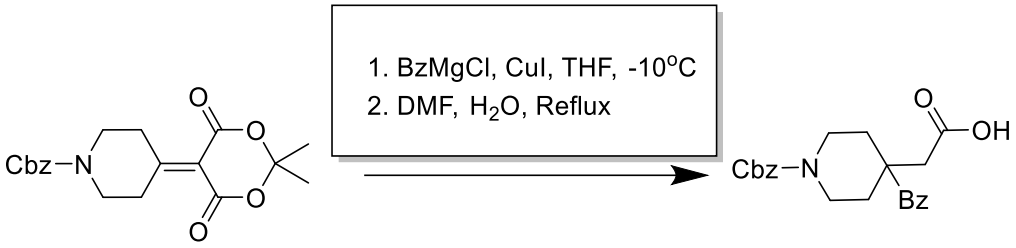

Chu, G.-H.; Le Bourdonnec, B.; Gu, M.; Saeui, C. T.; Dolle, R. E. General and Efficient Synthetic Approach to Novel Tricyclic Spiroketones. *Tetrahedron* **2009**, *65* (27), 5161-5167. https://doi.org/10.1016/j.tet.2009.04.094

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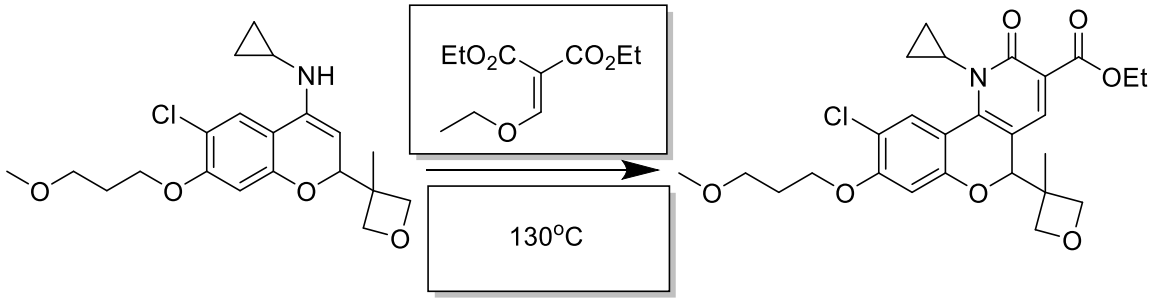
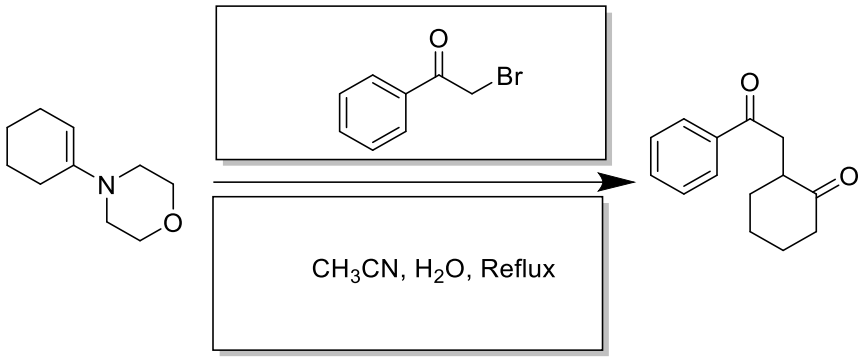


Mammoliti, O.; Palisse, A.; De Blieck, A.; Joannesse, C.; Allart, B.; Laruelle, C.; Jaunet, A.; De Munck, T.; Van der Plas, S.; Duthion, B.; Catana, C.; Christophe, T.; Houvenaghel, N.; Porte, V.; Jimenez, J.-M.; Beirinckx, F.; Iwens, A.; Chypre, M.; De Rijck, K.; Vandervoort, N.; Nelles, L.; Clément-Lacroix, P.; Delachaume, C.; Belleville, C.; Oste, L.; Borgonovi, M.; Wakselman, E.; Jans, M.; Hue-Perron, J.; Saniere, L.; Brys, R.; Andrews, M. Discovery and Characterization of GLPG3808, a PAPD5/7 Inhibitor for

11b.1.10



Pospelov, E. V.; Sukhorukov, A. Y. Accessing NH-Pyrrolidines from 1,4-Dicarbonyl Compounds via Catalytic Dioxime Cyclization. *J. Org. Chem.* **2026**, *91* (20), 7002-7012. https://doi.org/10.1021/acs.joc.6c00493

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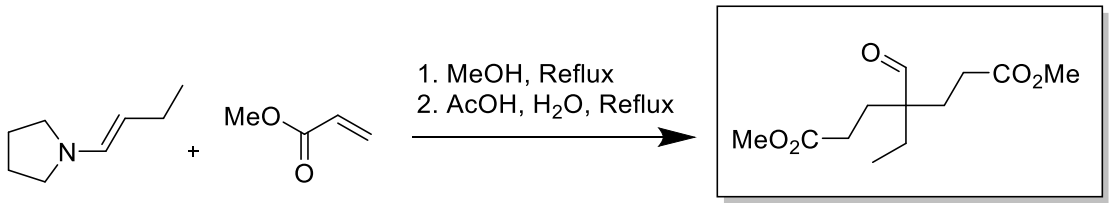
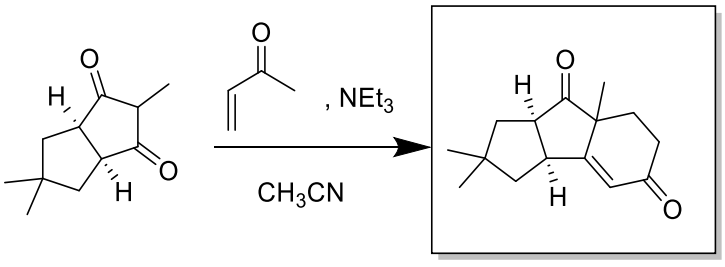


Hint: The acid in step 2 is used to remove a functional group.

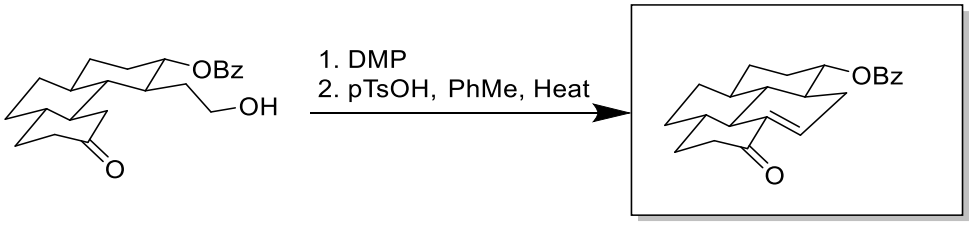
Zhang, L.; Lang, Y.; Luo, Z.; Han, X.; Zeng, H.; Li, C.-J. Precision Indole Skeletal Editing for Single-Carbon Replacement. *Science* **2026**, *392* (6797), 512-518. https://doi.org/10.1126/science.aec3587

11b.1.12



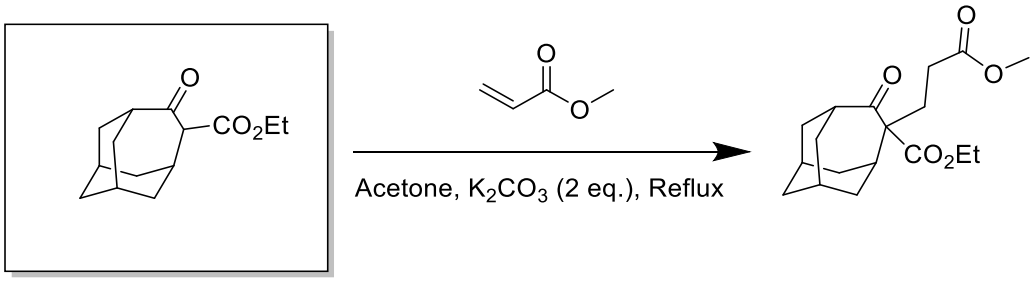
Siekmeyer, B.; Lübken, D.; Bajerke, K.; Bernhardt, B.; Schreiner, P. R.; Kalesse, M. Total Synthesis of (−)-Antroalbocin A Enabled by a Strain Release-Controlled Photochemical 1,3-Acyl Shift. *Org. Lett.* **2022**, *24* (31), 5812–5816.
https://doi.org/10.1021/acs.orglett.2c02347

11b.1.13



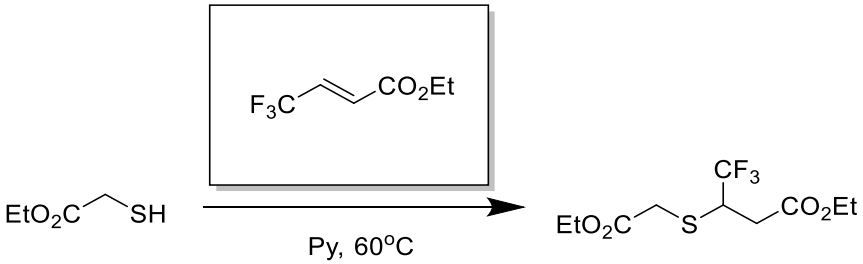
Roosen, P. C.; Karns, A. S.; Ellis, B. D.; Vanderwal, C. D. Evolution of a Short and Stereocontrolled Synthesis of (+)-7,20-Diisocyanoadociane. *J. Org. Chem.* **2022**, *87* (2), 1398–1420. https://doi.org/10.1021/acs.joc.1c02700

11b.1.14



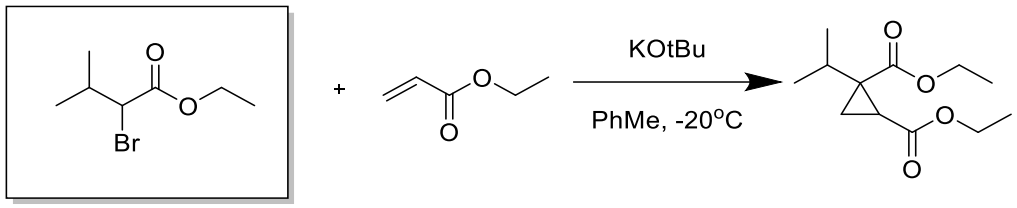
Tkachenko, I. M.; Mankova, P. A.; Rybakov, V. B.; Golovin, E. V.; Klimochkin, Y. N. Wagner–Meerwein Type Rearrangement in 5-Oxohomoadamantane Series. *Org. Biomol. Chem.* **2020**, *18* (3), 465–478. https://doi.org/10.1039/C9OB02060H

11b.1.15



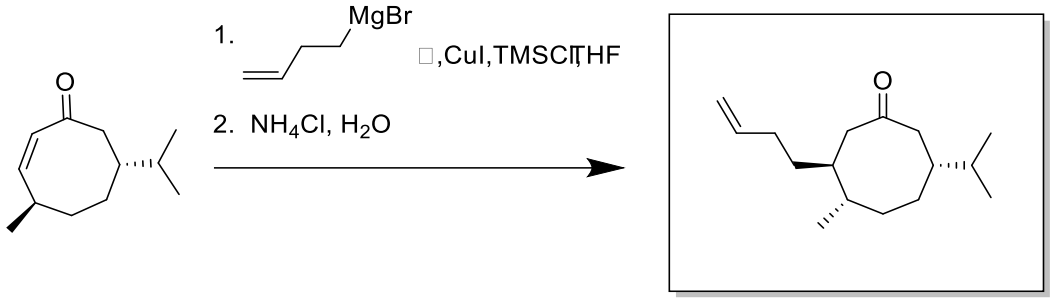
Redka, M. O.; Dovhaniuk, N.; Blahun, O.; Liashuk, O. S.; Hurieva, A. M.; Lesyk, D.; Skrypnik, D.; Holota, Y.; Durylin, D.; Borysko, P.; Kondratov, I. S.; Grygorenko, O. O. Synthesis and Physicochemical Characterization of 5-Trifluoromethyl-Substituted Tetrahydrofurans and Tetrahydrothiophenes. *Eur. J. Org. Chem.* **2026**, *29* (3), e202501086. https://doi.org/10.1002/ejoc.202501086

11b.1.16



Starkenmann, C.; Cayeux, I.; Brauchli, R.; Mayenzet, F. Hemisynthesis of Dihydroumbellulols from Umbellulone: New Cooling Compounds. *J. Agric. Food Chem.* **2011**, *59* (2), 677–683. https://doi.org/10.1021/jf103989j

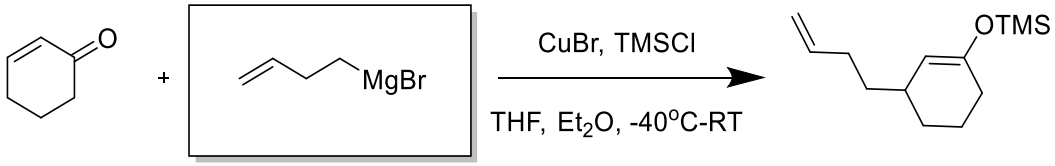
11b.1.17



Note: Think carefully about the stereochemistry of the product.

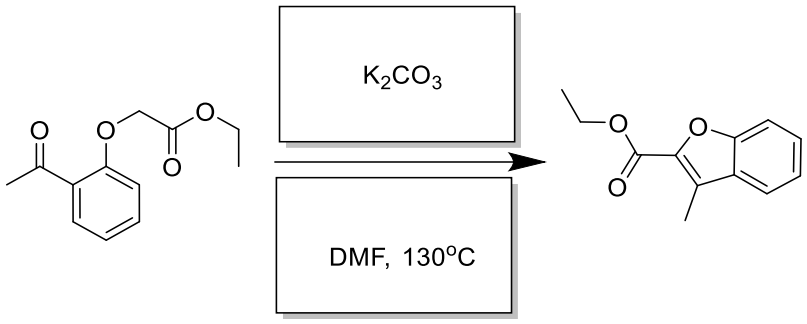
Wang, X.-L.; Lu, Y.-Y.; Wang, J.; Wang, X.; Yao, H.-Q.; Lin, G.-Q.; Sun, B.-F. A Novel Synthetic Approach to the Bicyclo[5.3.1]undecan-11-one Framework of Vinigrol. *Org. Biomol. Chem.* **2014**, *12* (22), 3562-3566. https://doi.org/10.1039/C4OB00046C

11b.1.18



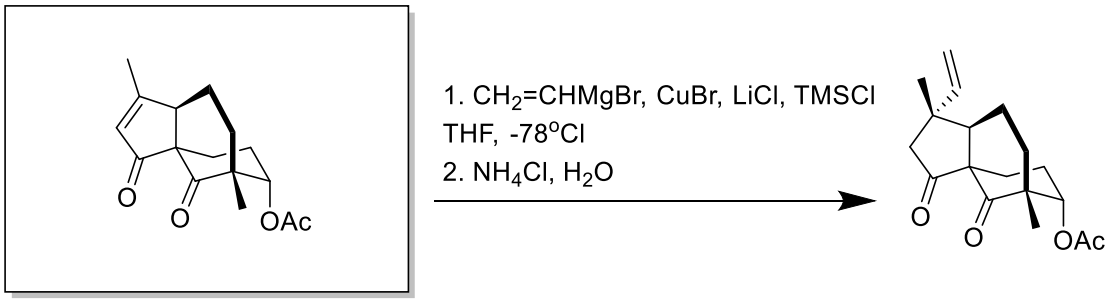
Vulovic, B.; Trmcic, M.; Matovic, R.; Saicic, R. N. Cyclization Reactions of Oxyallyl Cation. A Method for Cyclopentane Ring Formation. *Org. Lett.* **2019**, *21* (23), 9618–9621. https://doi.org/10.1021/acs.orglett.9b03791

11b.1.19



Eldehna, W. M.; Tawfik, H. O.; Nafie, M. S.; Al Kamaly, O.; El-Hamaky, A. A.; El Hassab, M. A.; Elsayed, Z. M.; Elnaggar, Y. S. R.; Al-Karmalawy, A. A.; Di Giacomo, V.; Balaha, M. Novel Benzofuran-Conjugated Indolin-2-Ones as Anticancer Agents: Design, Synthesis, Biological Assessments, and Molecular Modeling Insights. *Bioorg. Chem.* **2025**, *160*, 108494. https://doi.org/10.1016/j.bioorg.2025.108494

11b.1.20



Ninomiya, D.; Nagasawa, S.; Iwabuchi, Y. A Unified Approach to Highly Functionalized Clovane-Type Terpenoids: Enantiocontrolled Total Synthesis of Rumphellclovane E and Sarinfacetamides A and B. *Chem. Sci.* **2025**, *16* (34), 15707-15713. https://doi.org/10.1039/D5SC04197J

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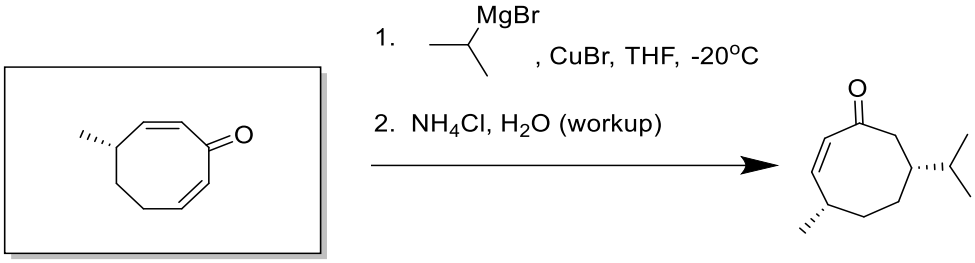

Wang, X.-L.; Lu, Y.-Y.; Wang, J.; Wang, X.; Yao, H.-Q.; Lin, G.-Q.; Sun, B.-F. A Novel Synthetic Approach to the Bicyclo[5.3.1]undecan-11-one Framework of Vinigrol. *Org. Biomol. Chem.* **2014**, *12* (22), 3562-3566. https://doi.org/10.1039/C4OB00046C

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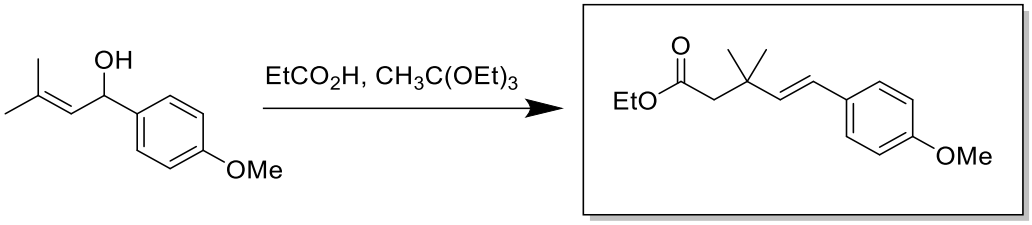
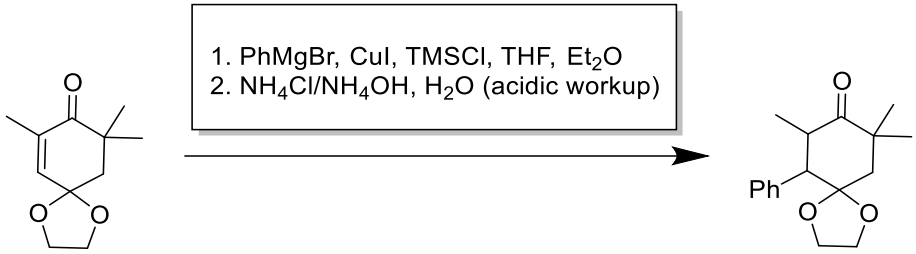


Tsai, S.; Huang, Y.; Chou, C. Carboxylate-Directed Palladium-Catalyzed Regioselective Mizoroki-Heck Alkenylation of *γ* , *δ* -Unsaturated Carboxylic Acids. *Adv Synth Catal* **2023**, *365* (5), 699–703. https://doi.org/10.1002/adsc.202201317

11b.1.23



TMSCl is used to trap the carbonyl oxygen as a silyl ether but upon acidic workup, the TMS group is removed. Learners in introductory organic chemistry courses may not know to do this.

Xiong, J.; Wang, Y.; Tang, X. Binaphthalene-Modified C-Scorpionate Zinc Catalysts for Ring-Opening Polymerization of Bio-Based γ-Ketolactones to High-Molar-Mass Degradable Polyesters. *Angew. Chem. Int. Ed.* **2026**, *65* (3), e17535. https://doi.org/10.1002/anie.202517535

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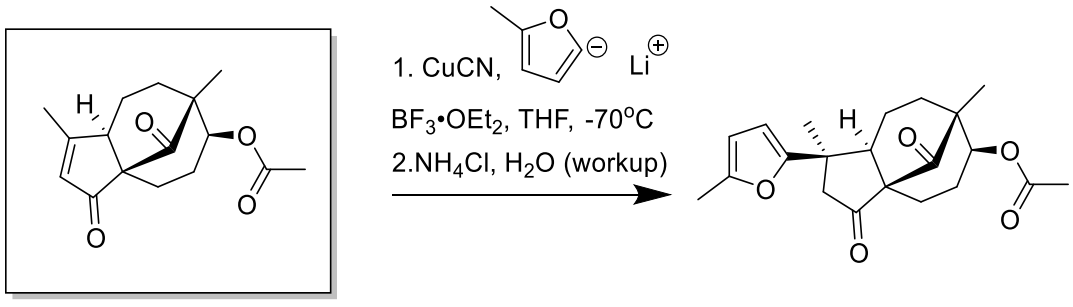

Ninomiya, D.; Nagasawa, S.; Iwabuchi, Y. A Unified Approach to Highly Functionalized Clovane-Type Terpenoids: Enantiocontrolled Total Synthesis of Rumphellclovane E and Sarinfacetamides A and B. *Chem. Sci.* **2025**, *16* (34), 15707-15713. https://doi.org/10.1039/D5SC04197J

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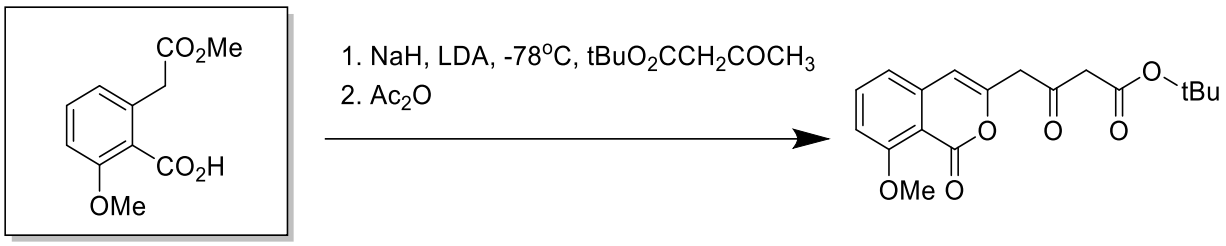
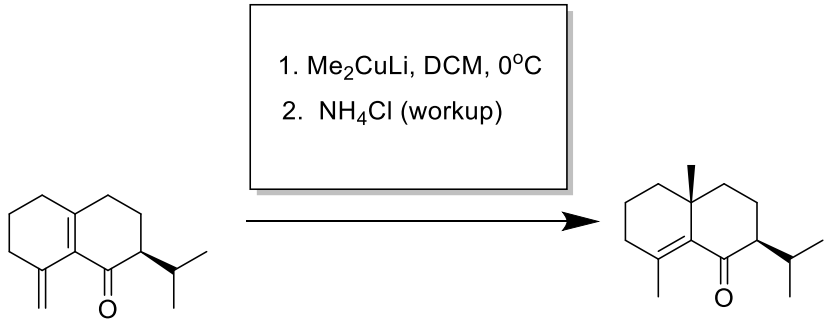


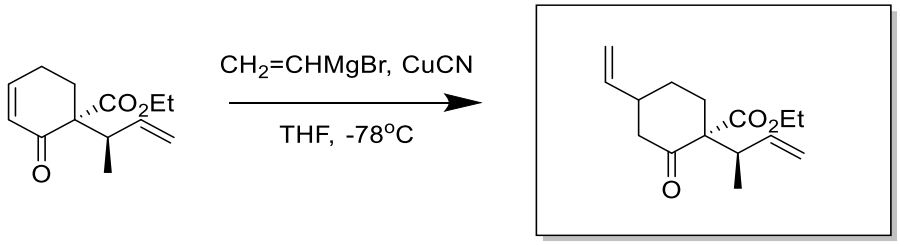
Zhou, J.-L.; Nie, Q.-Y.; Hou, X.-F.; Zheng, K.; Hong, R.; Tang, G.-L. Multienzyme Cascade Catalyzed Skeleton Rearrangement in a Caged Polyketide Biosynthesis. *Org. Lett.* **2025**, *27* (1), 376–380. https://doi.org/10.1021/acs.orglett.4c04412

11b.1.26



Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C–H Oxidations. *Nature* **2009**, *459* (7248), 824–828. https://doi.org/10.1038/nature08043

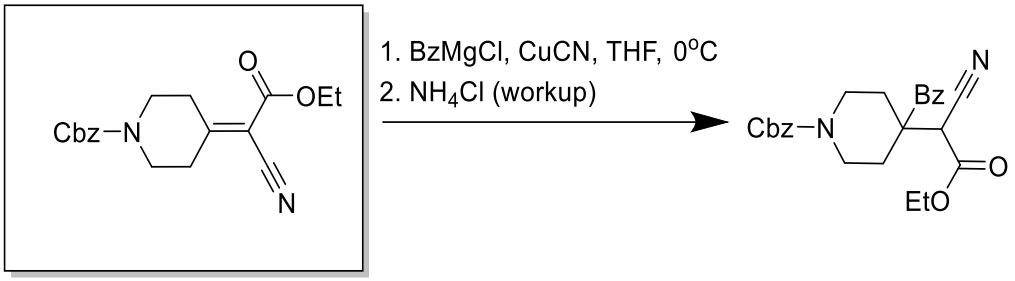
11b.1.27



Note: Assume the reaction is followed by an acidic workup.

Mao, H.-K.; Wang, Q.; Xu, J. Enantioselective Total Synthesis of Fortalpinoid Q via a $TEMPO^+$ BF_4^- -Mediated Dehydrative Nazarov Cyclization. *J. Am. Chem. Soc.* **2025**, *147* (11), 9079–9084. https://doi.org/10.1021/jacs.5c00319

11b.1.28

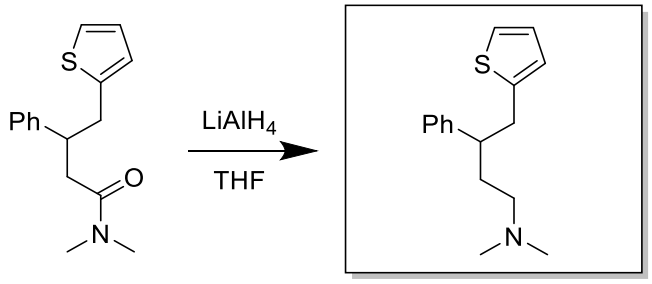


Chu, G.-H.; Le Bourdonnec, B.; Gu, M.; Saeui, C. T.; Dolle, R. E. General and Efficient Synthetic Approach to Novel Tricyclic Spiroketones. *Tetrahedron* **2009**, *65* (27), 5161-5167. https://doi.org/10.1016/j.tet.2009.04.094

Section 12 – Box-Type Questions

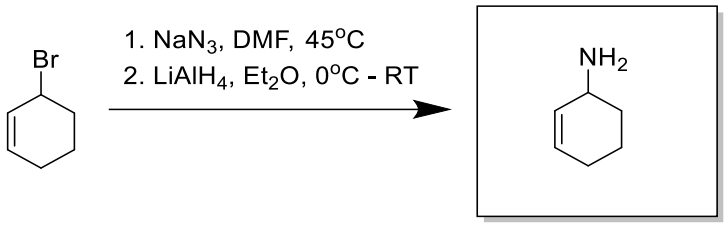
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

12.1.1



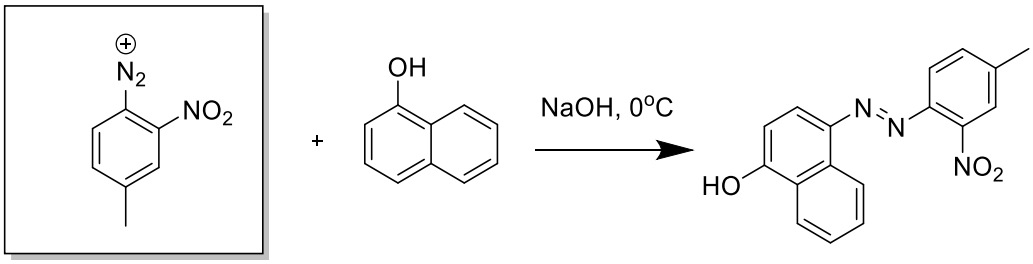
Gu, Y.; Ma, R.; Zuo, S.; Liu, G.; Li, G.; Yu, R.; Xiong, D.; Xu, X.; Walsh, P. J.; Mao, J. Raising the *p*K_a_ Limit of Pronucleophiles in 1,4-Additions via Heterobimetallic Alkali-Metal Catalysis. *ACS Catal.* **2026**, *16* (9), 8619-8632. https://doi.org/10.1021/acscatal.6c01195

12.1.2



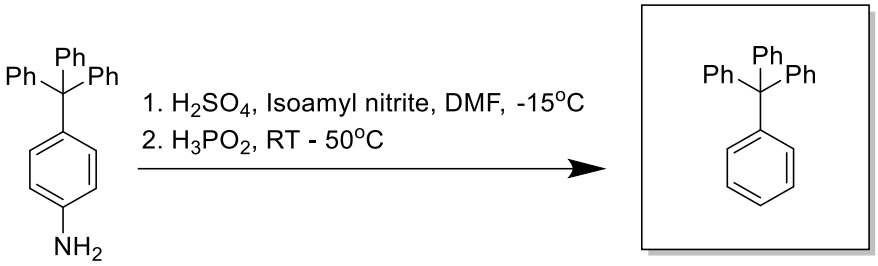
Nguyen, S. T.; Zhu, Q.; Knowles, R. R. PCET-Enabled Olefin Hydroamidation Reactions with *N*-Alkyl Amides. *ACS Catal.* **2019**, *9* (5), 4502-4507. https://doi.org/10.1021/acscatal.9b00966

12.1.3



Razeghi, R.; Kazemi, F.; Kaboudin, B.; Olyaei, A.; Yokomatsu, T. Synthesis and Characterization of Novel Photochromic and pH-Sensitive Colorimetric Hydrogel Based on Azobenzene. *Can. J. Chem.* **2021**, *99* (4), 368-381. https://doi.org/10.1139/cjc-2020-0369

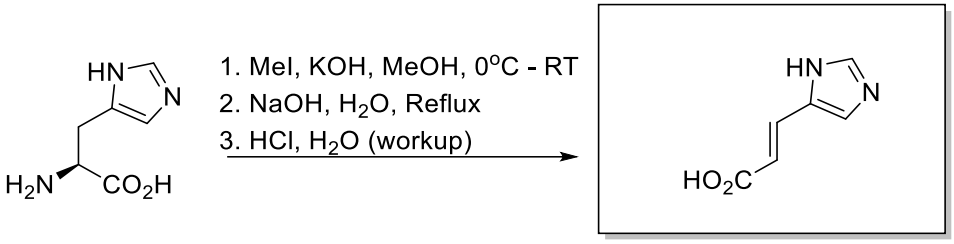
12.1.4



Note: Isoamyl nitrite is analogous to sodium nitrite.

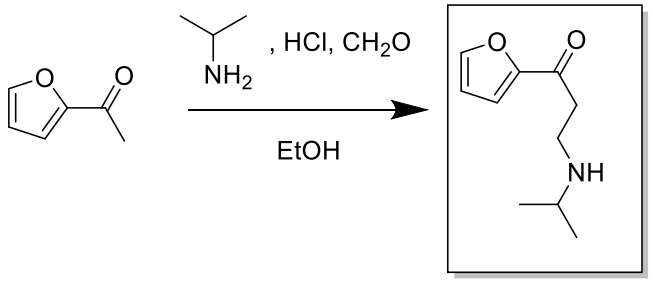
Bulut, A.; Doğan, N.; Kirpi, E.; Zorlu, Y.; Yücesan, G. A Systematic Look at Structural Diversity of Metal Phosphonates. *Eur. J. Inorg. Chem.* **2024**, *27* (13), e202300699. https://doi.org/10.1002/ejic.202300699

12.1.5



Valeev, F. A.; Salikhov, Sh. M.; Krasnoslobodtseva, O. Y.; Sharipov, B. T.; Spirikhin, L. V.; Tolstikov, G. A. Synthesis of *N*-Methyl Urocanates of Hydroxyderivatives of Isocembrol. *Chem. Nat. Compd.* **2007**, *43* (2), 143-148. https://doi.org/10.1007/s10600-007-0065-6

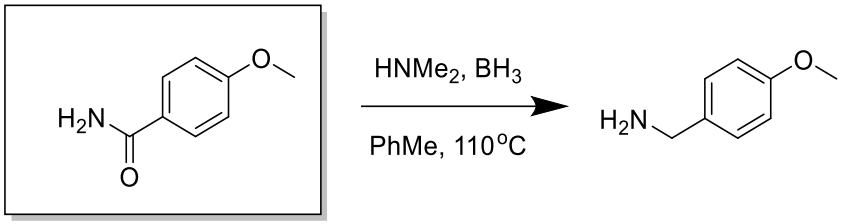
12.1.6



Note: Assume there was a basic workup following the reaction.

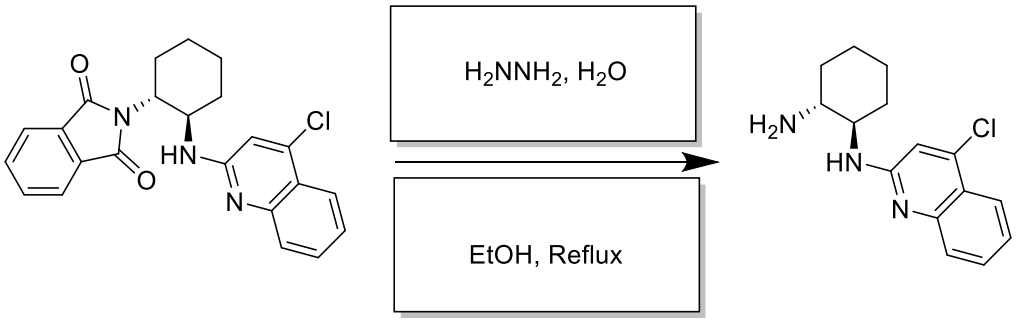
Lewis, D.; Zhang, Y.; Prisinzano, T.; Dersch, C. M.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. Further Exploration of 1-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}piperazine (GBR 12909): Role of N-Aromatic, N-Heteroaromatic, and 3-Oxygenated N-phenylpropyl Substituents on Affinity for the Dopamine and Serotonin Transporter. *Bioorg. Med. Chem. Lett*. **2003**, *13* (7), 1385–1389. https://doi.org/10.1016/S0960-894X(03)00108-2

12.1.7



Chowdhury, D.; Mukherjee, A. Unlocking an Additive-Free and Catalyst-Free Dual Approach for Reduction of Amides to Amines. *Chem. Commun.* **2025**, *61* (8), 1605-1608. https://doi.org/10.1039/D4CC04606D

12.1.8



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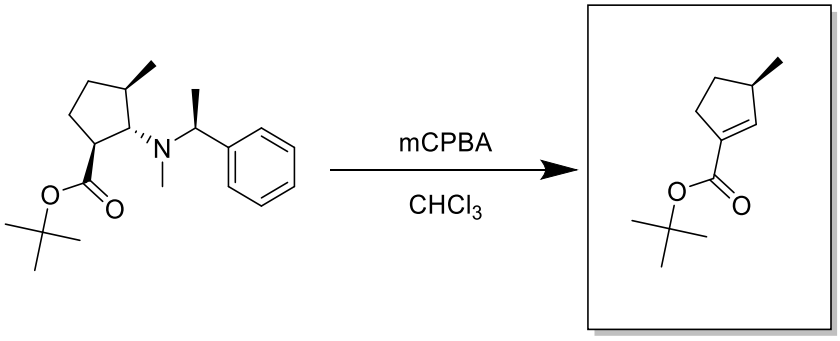
12.1.9



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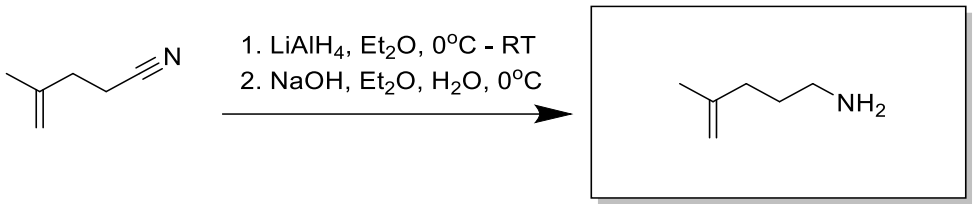

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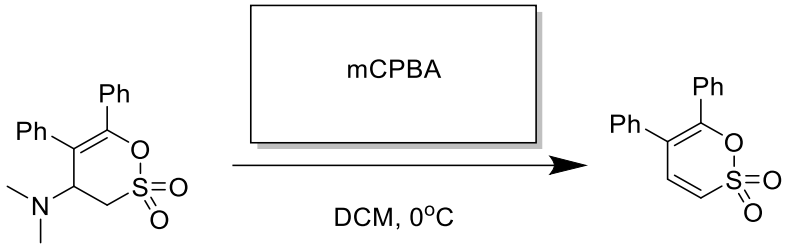

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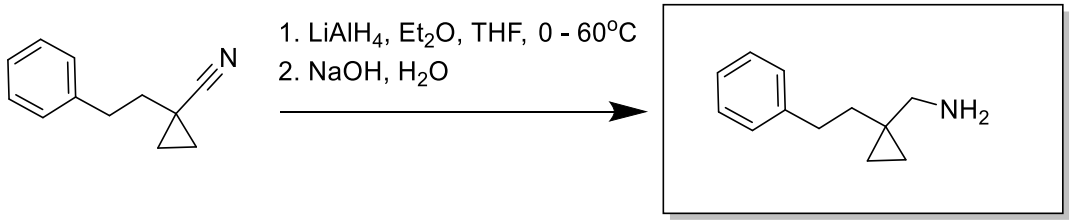

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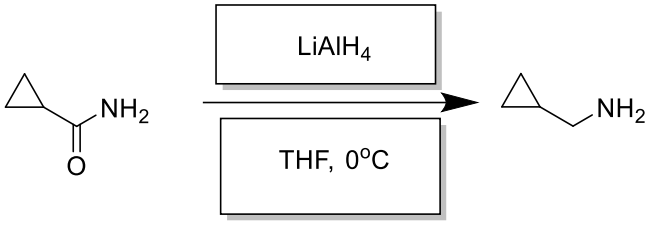

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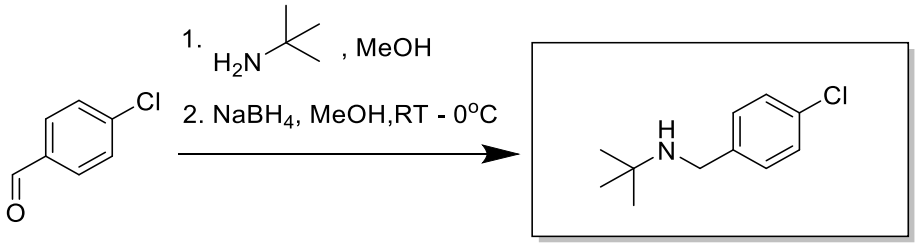

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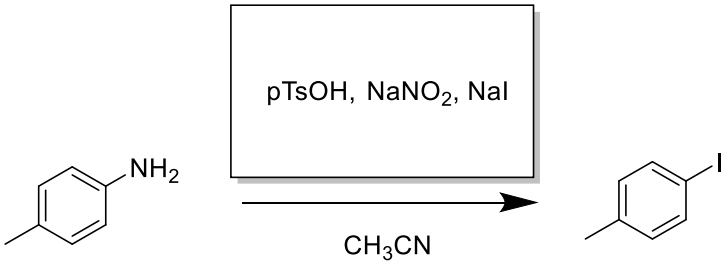

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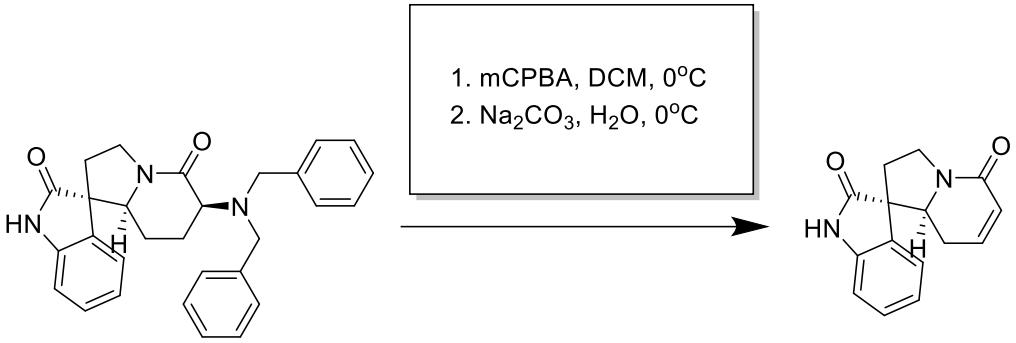

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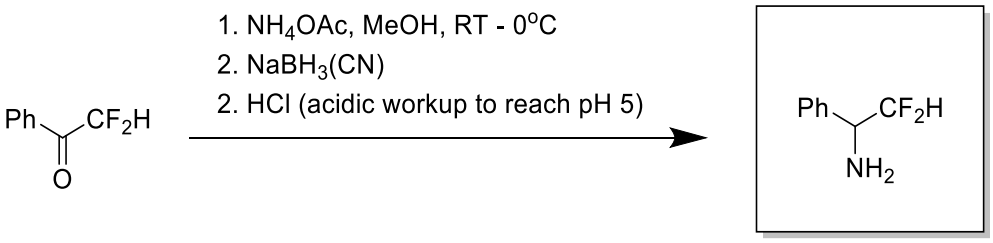

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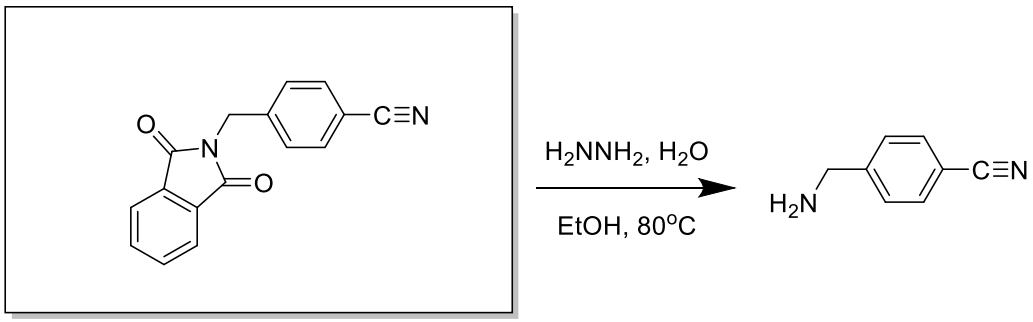

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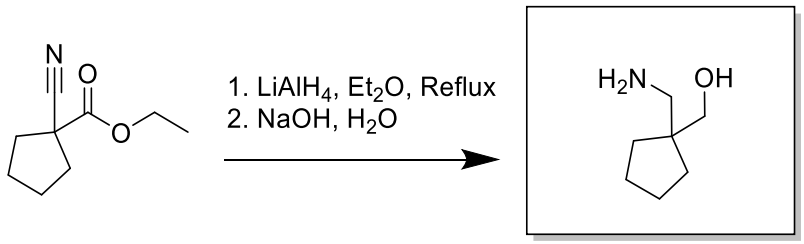

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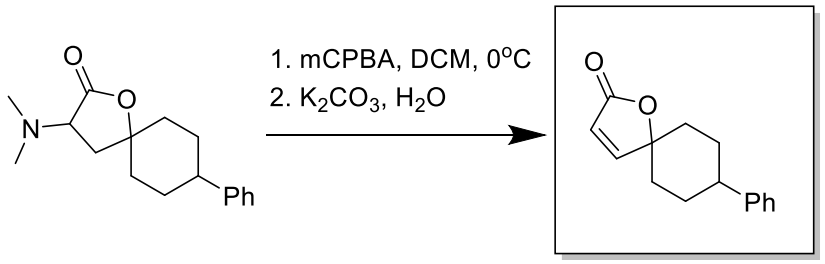

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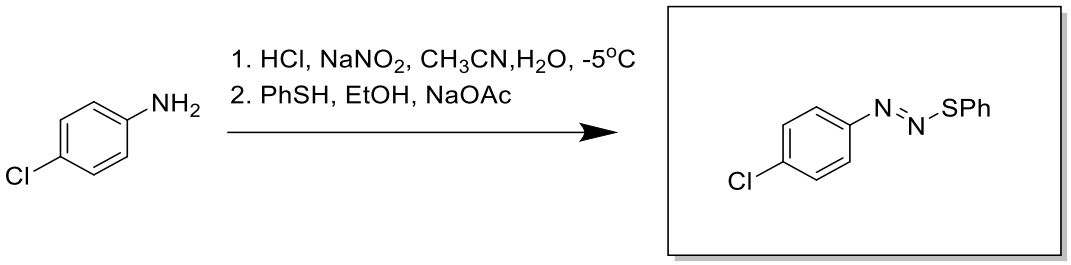

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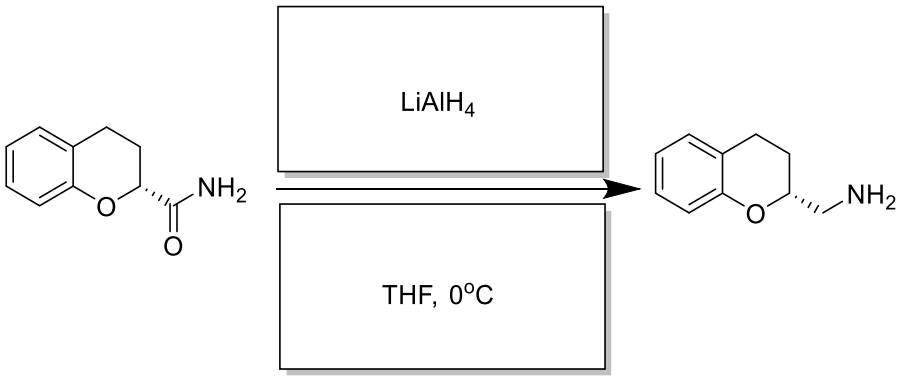

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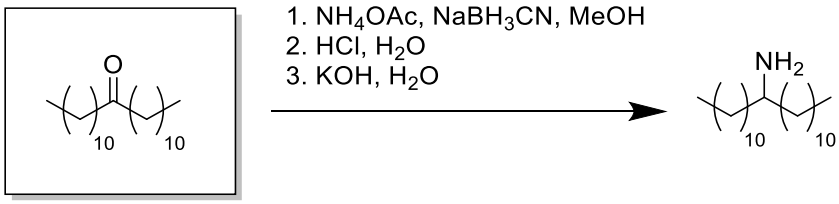

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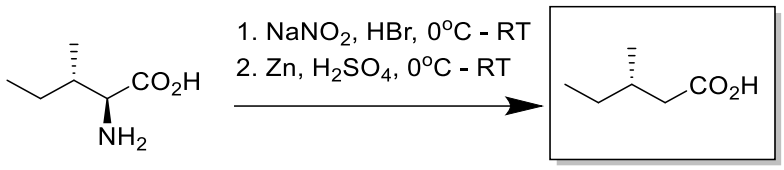

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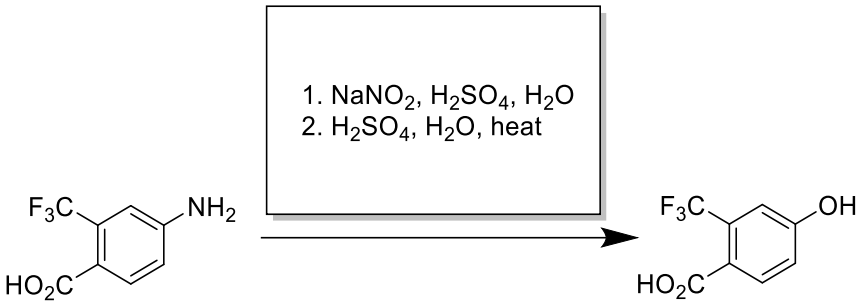

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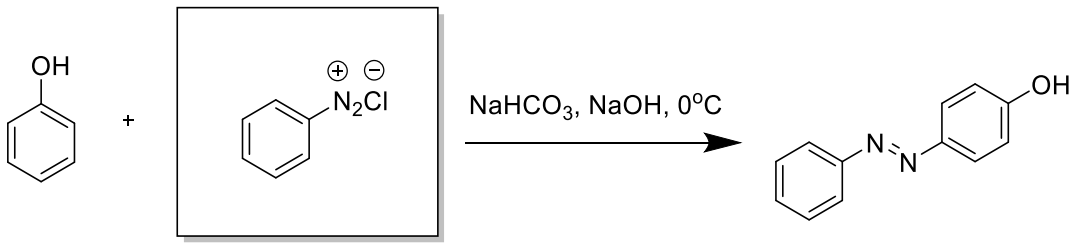

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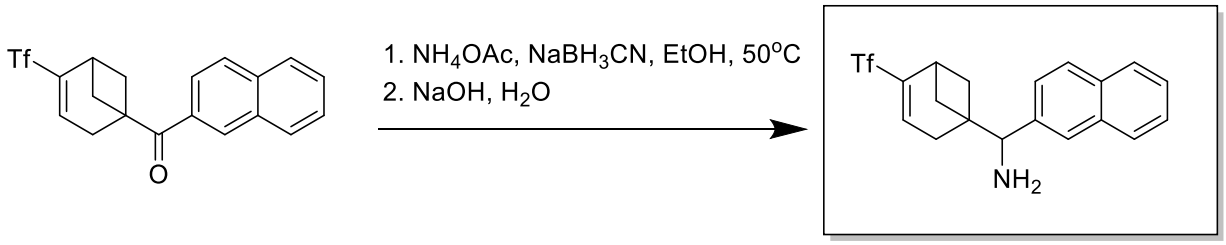

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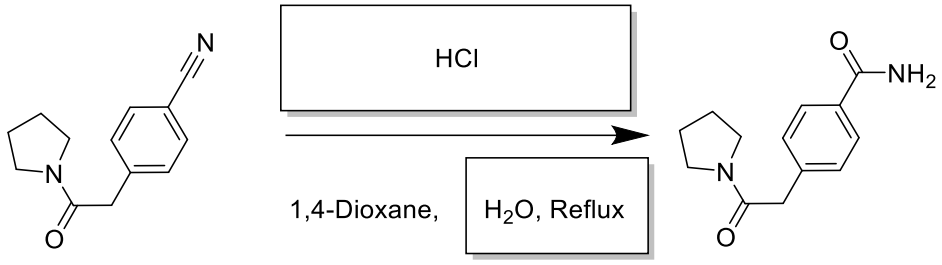

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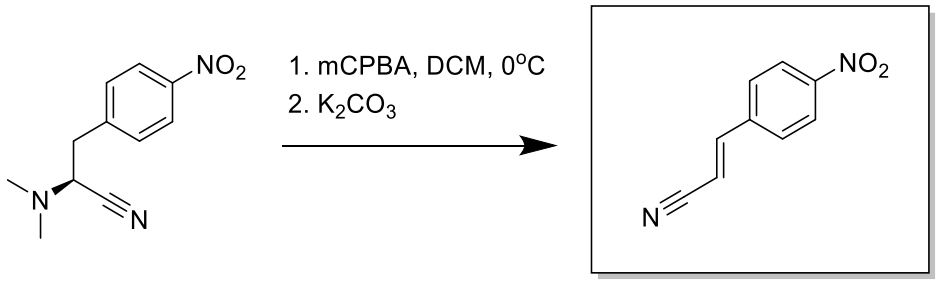

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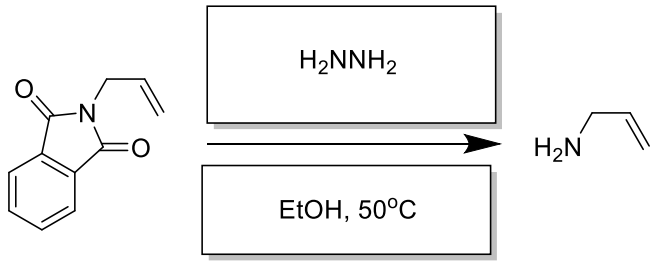

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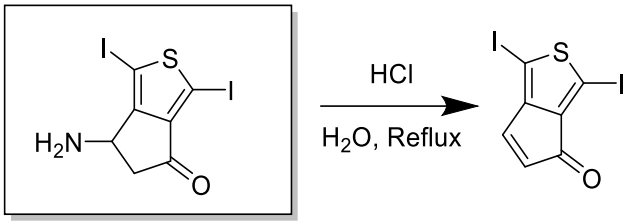

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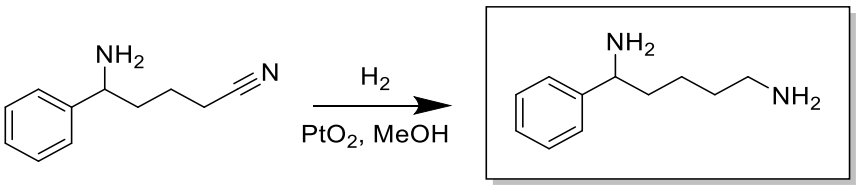

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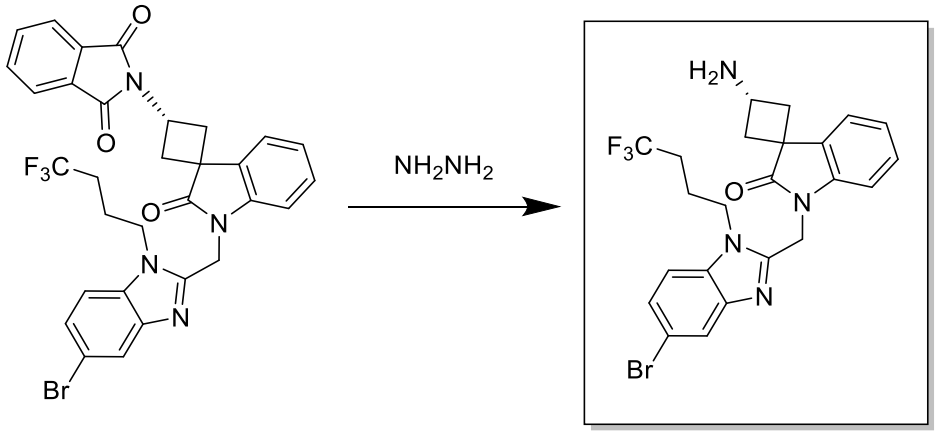

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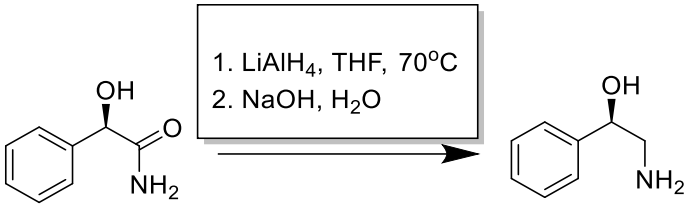

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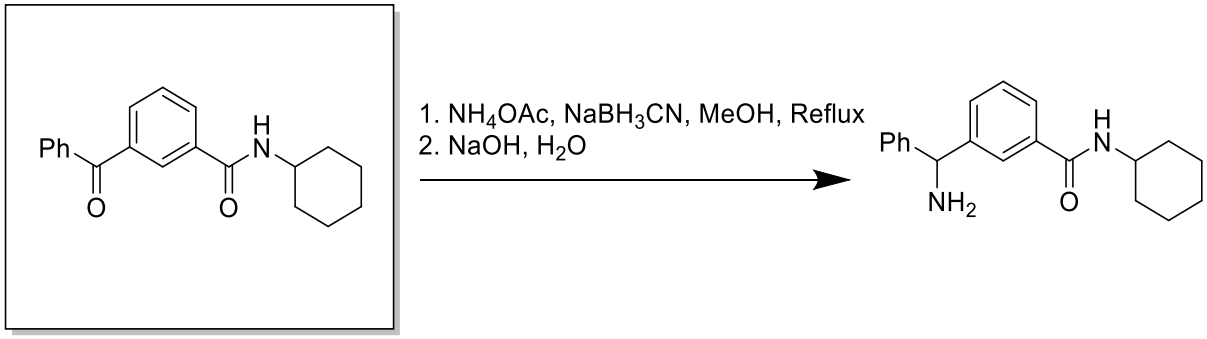

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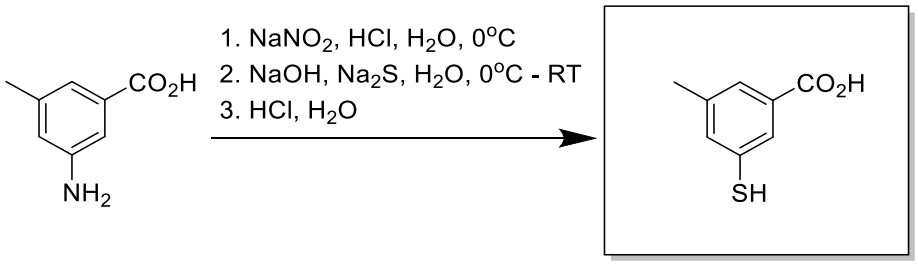

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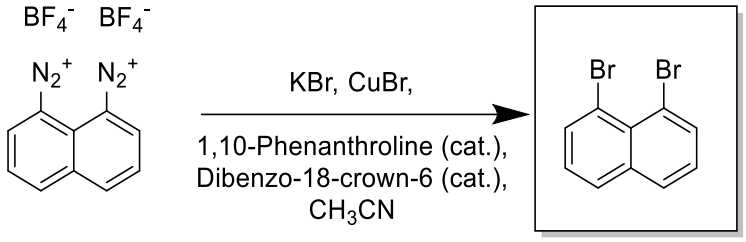

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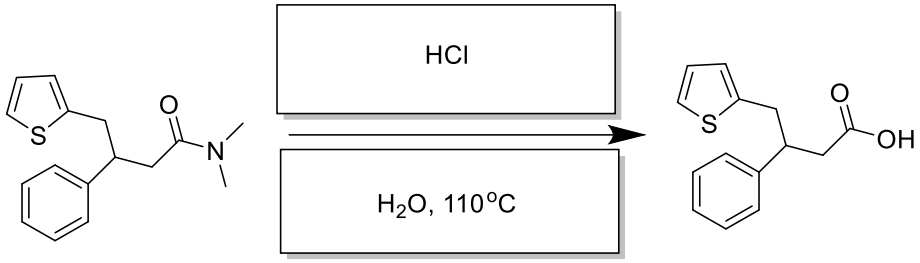

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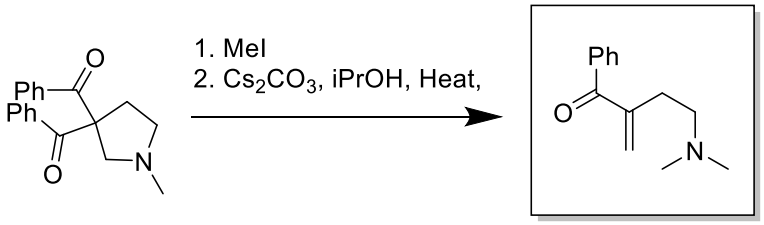

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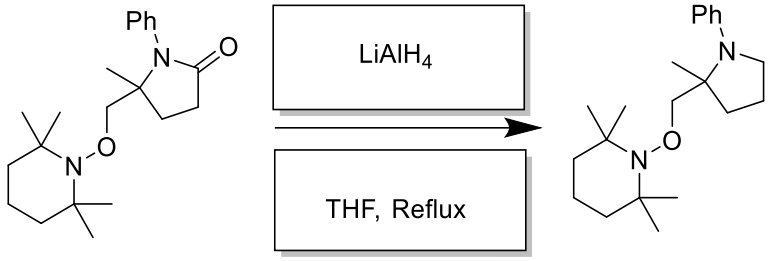
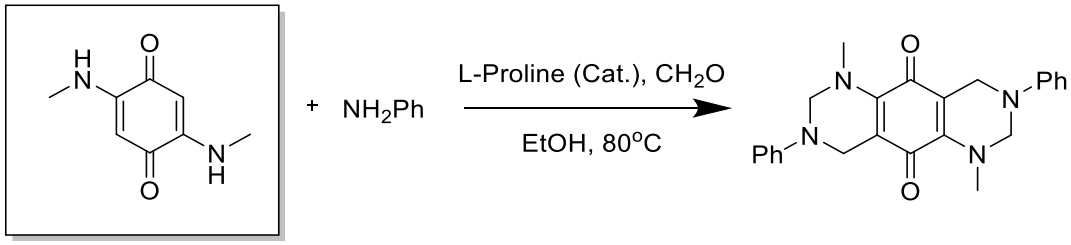


Suryawanshi, S. M.; Singh, M.; Samanta, R. C. Electrochemical Generation of *N*-Centered Radicals and Their Reactivity Toward Cyclization and Subsequent C−C Bond Cleavage. *Helv. Chim. Acta* **2026**, *109* (4), e00225. https://doi.org/10.1002/hlca.202500225

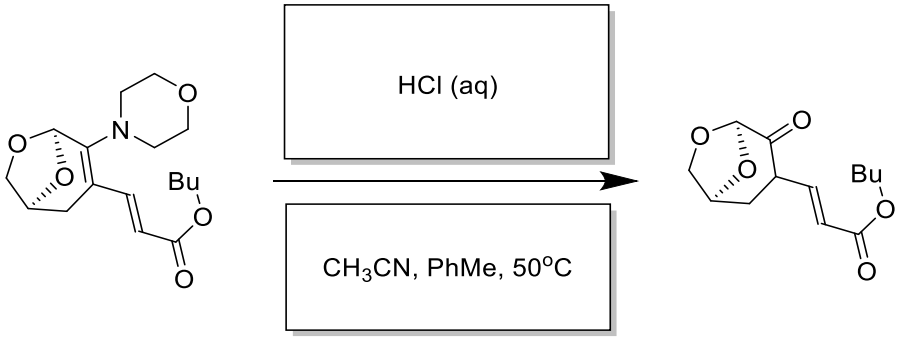
12.1.42



Note: The L-Proline catalyst is an acid catalyst.

Van Hoof, M.; Bynens, L.; Daelemans, B.; Rodríguez González, M. C.; Van Meervelt, L.; De Feyter, S.; Dehaen, W. Octahydropyrimido[4,5-g]quinazoline-5,10-diones: Their Multicomponent Synthesis, Self-Assembly on Graphite and Electrochemistry. *Chem. Commun*. **2022**, *58* (55), 7686–7689. https://doi.org/10.1039/D2CC02070J

12.1.43

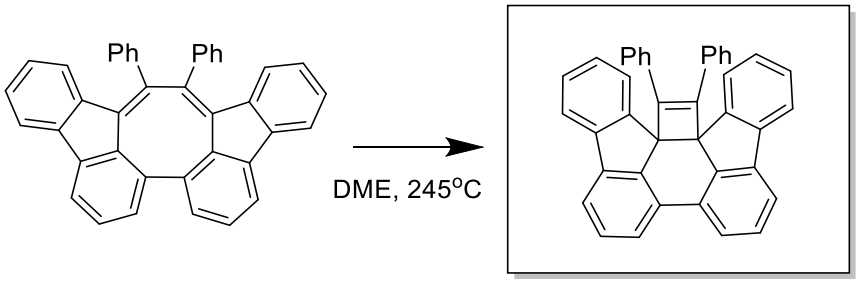


Lamb, O. J.; Podversnik, H.; Puschnig, J.; Greatrex, B. W. Palladium-Mediated Substitution of LGO and Cyrene via Stable Halogenated Enamines. *ChemistrySelect* **2026**, *11* (3), e07470. https://doi.org/10.1002/slct.202507470

Section 13 – Box-Type Questions

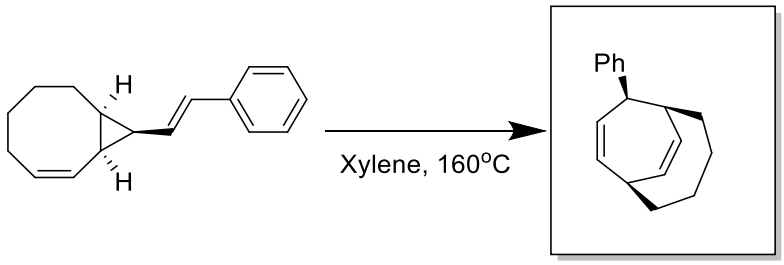
For each question, identify the missing reactant, predict the major product, or determine the reagent(s) required to achieve the indicated transformation. Your answers may differ from those provided; focus on whether your solution employs a reasonable strategy and appropriate chemistry. Be sure to indicate stereochemistry where applicable. Discuss your answers with classmates and your instructor to strengthen your understanding.

13.1.1



Chen, H.-H.; Liu, C.-H.; Ou, W.-T.; Huang, K.-H.; Yang, C.-J.; Cheng, M.-J.; Wu, Y.-T. 1,8-Di(2-ethynylaryl)biphenylenes: Palladium-Catalyzed Intramolecular Cycloisomerization and Subsequent Thermal Rearrangement. *Org. Lett.* **2025**, *27* (46), 12886-12891. https://doi.org/10.1021/acs.orglett.5c04302

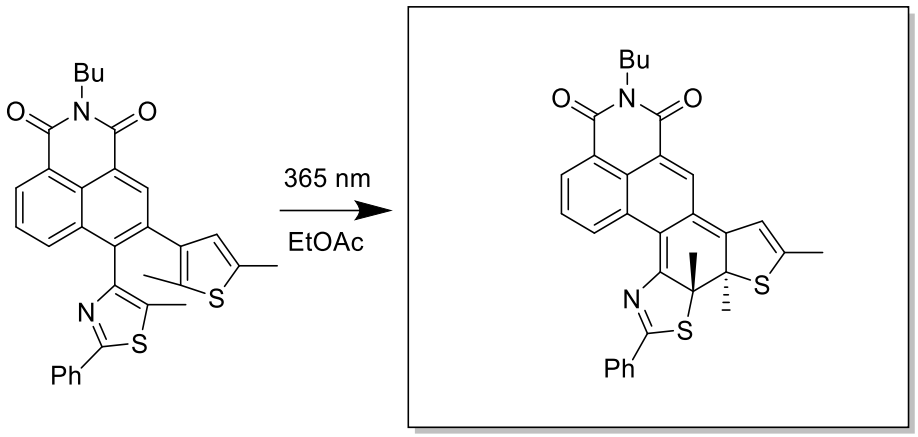
13.1.2



Hint: A bicyclic product is made.

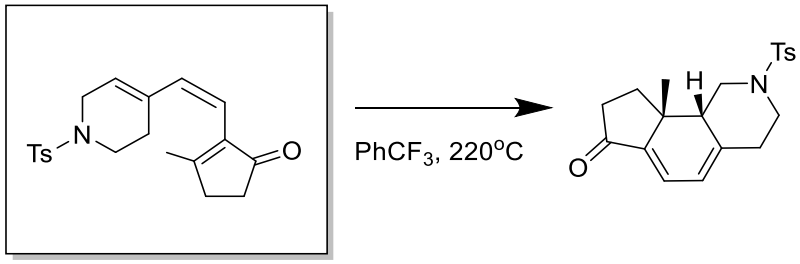
Fang, Z.; Ma, Y.; Liu, S.; Bai, H.; Li, S.; Ning, Y.; Zanoni, G.; Liu, Z. Silver-Catalyzed [4 + 3] Cycloaddition of 1,3-Dienes with Alkenyl-*N*-Triftosylhydrazones: A Practical Approach to 1,4-Cycloheptadienes. *Org. Chem. Front.* **2022**, *9* (16), 4426-4434. https://doi.org/10.1039/D2QO00806H

13.1.3



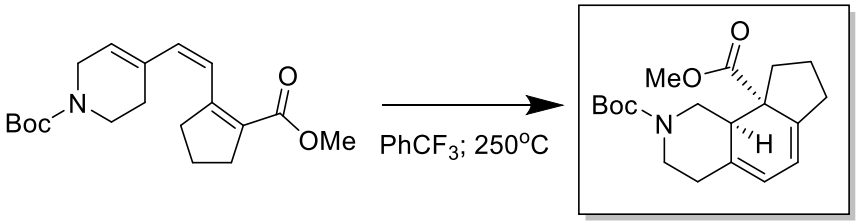
Orhan, E.; Köse, M.; Yazan, T. The Synthesis of New 3,4-(Bisaryl)-1,8-naphthalimide and 2,3-(Bisaryl)-7*H*-benzimidazo[2,1-*a*]benzo[*d*]isoquinolin-7-one Compounds and an Investigation of Their Photochromic Properties. *Turk. J. Chem.* **2018**, *42* (4), 1086-1094. https://doi.org/10.3906/kim-1711-3

13.1.4



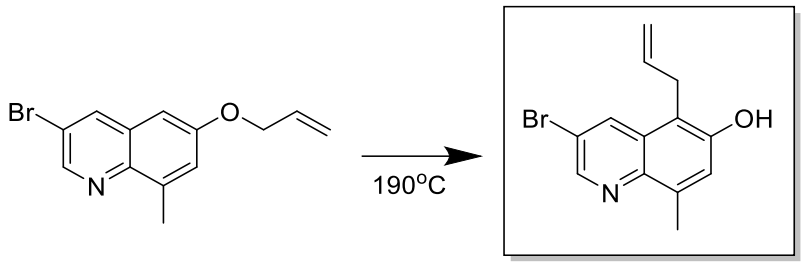
Krieger, J.-P.; Ricci, G.; Lesuisse, D.; Meyer, C.; Cossy, J. Efficient and Modular Synthesis of New Structurally Diverse Functionalized [*n*]Paracyclophanes by a Ring-Distortion Strategy. *Angew. Chem. Int. Ed.* **2014**, *53* (33), 8705-8708. https://doi.org/10.1002/anie.201401070

13.1.5



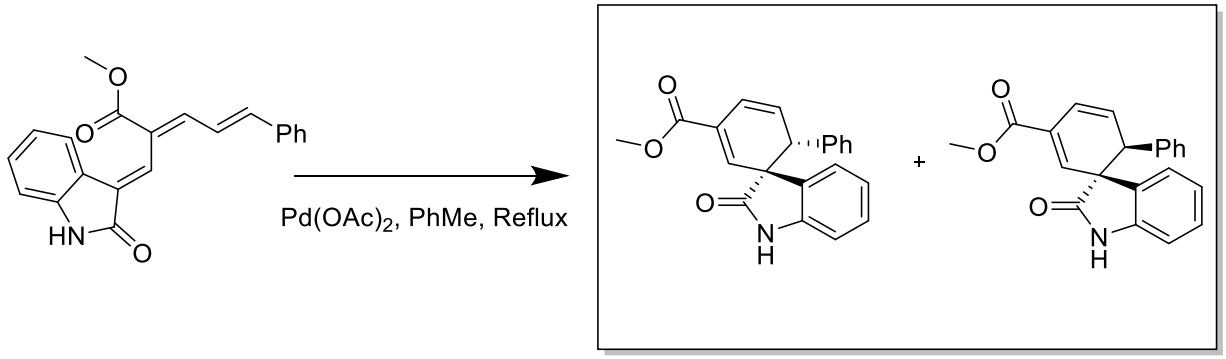
Krieger, J.-P.; Ricci, G.; Lesuisse, D.; Meyer, C.; Cossy, J. Efficient and Modular Synthesis of New Structurally Diverse Functionalized [*n*]Paracyclophanes by a Ring-Distortion Strategy. *Angew. Chem. Int. Ed.* **2014**, *53* (33), 8705-8708. https://doi.org/10.1002/anie.201401070

13.1.6



Murphy Kessabi, F.; Beaudegnies, R.; Quaranta, L.; Lamberth, C. Synthesis of Conformationally Locked Analogs of Quinolin-6-yloxyacetamide Fungicides. *Tetrahedron Lett.* **2016**, *57* (49), 5511-5513. https://doi.org/10.1016/j.tetlet.2016.10.104

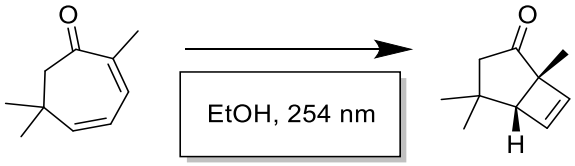
13.1.7



Note: Learners in introductory organic chemistry do not need to understand the catalytic role of $Pd(OAc)_2$ in this reaction.

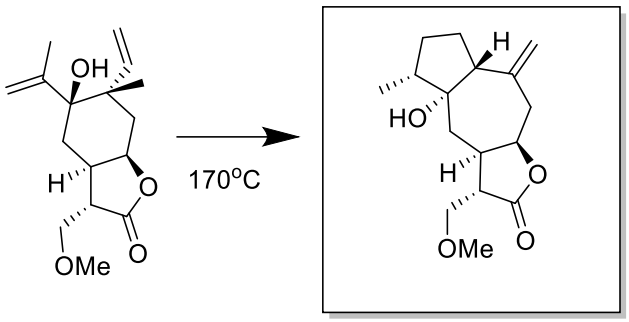
Kim, K. H.; Moon, H. R.; Lee, J.; Kim, J.; Kim, J. N. Diastereoselective Synthesis of Six-Membered Carbocyclic Spirooxindoles via 6π-Electrocyclization of 3-Dienylidene-2-oxindoles. *Adv. Synth. Catal.* **2015**, *357* (7), 1532-1544. https://doi.org/10.1002/adsc.201500260

13.1.8



Holl, M. G.; Lambert, T. H. Ring-Opening Carbonyl-Olefin Metathesis of Cyclobutenes. *ACS Catal.* **2022**, *12* (9), 4813-4817. https://doi.org/10.1021/acscatal.2c01188

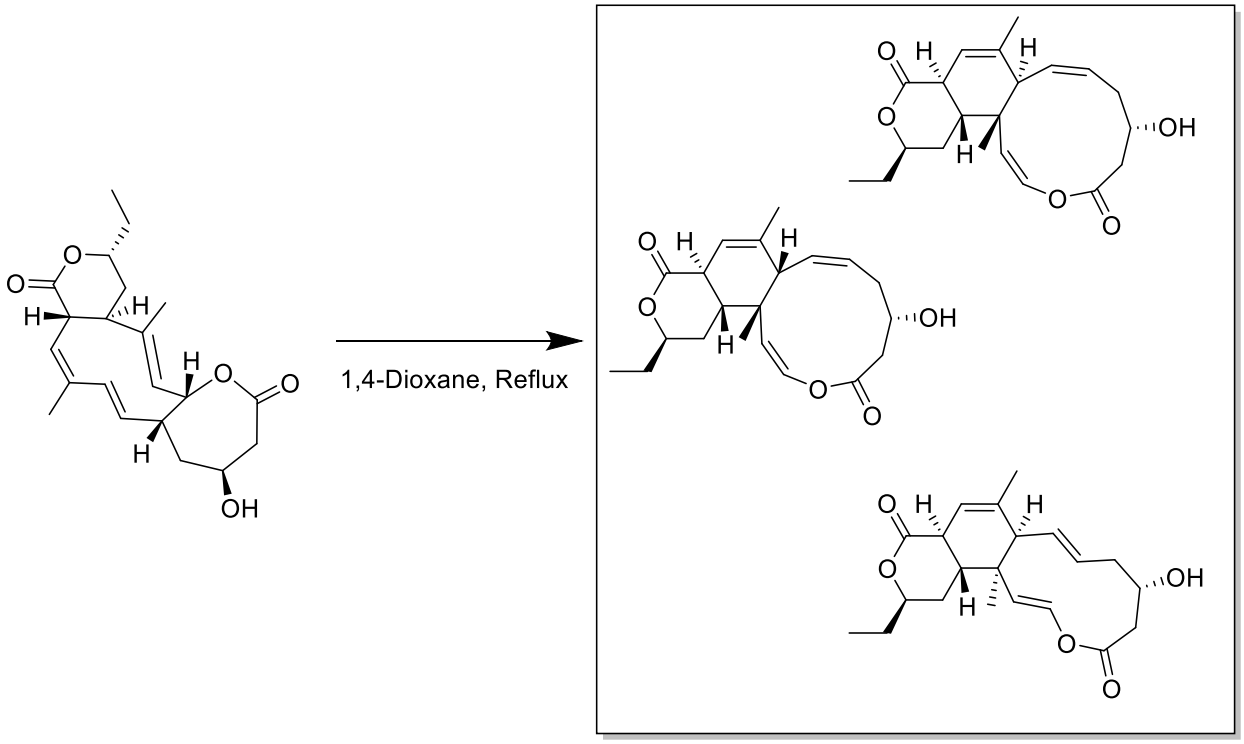
13.1.9



Hint: There is an oxy-Cope rearrangement followed by the formation of a five and seven-membered ring.

Demertzidou, V. P.; Kourgiantaki, M.; Zografos, A. L. Expanding Natural Diversity: Tailored Enrichment of the 8,12-Sesquiterpenoid Lactone Chemical Space through Divergent Synthesis. *Org. Lett.* **2024**, *26* (22), 4648-4653. https://doi.org/10.1021/acs.orglett.4c01374

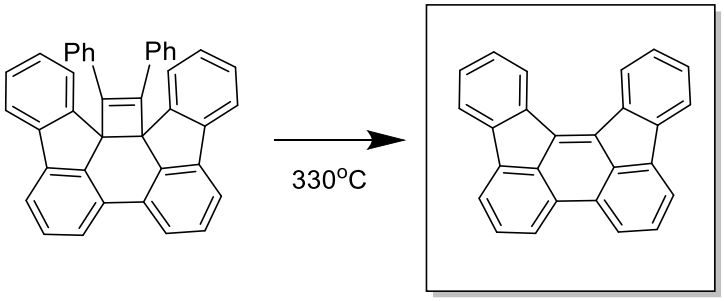
13.1.10



Hint: Three products are made, propose structures for all three products.

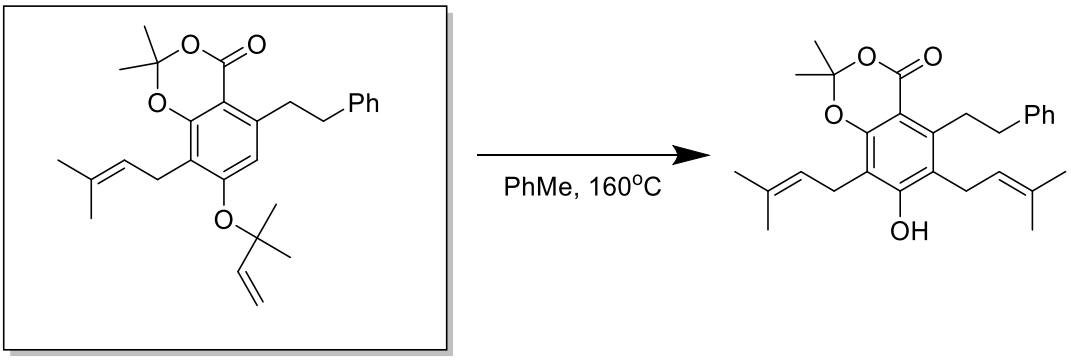
Decker, R. L.; Schray, D.; Pfeffer, H. I.; Grond, S.; Wagner, J. P. Conformations and Rearrangements of Collinolactone: Experiments and Theory on a Dynamic Cyclodecatriene. *Chem. Eur. J.* **2024**, *30* (10), e202303435. https://doi.org/10.1002/chem.202303435

13.1.11



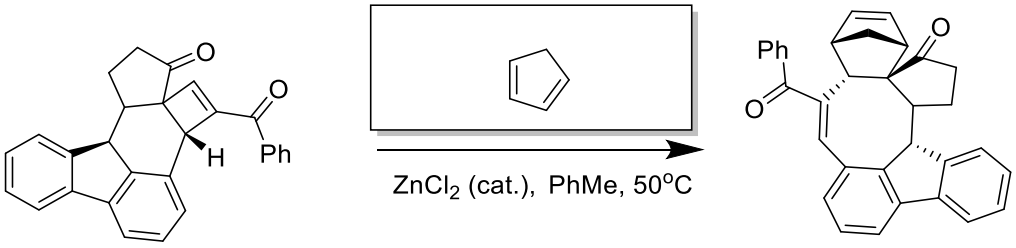
Chen, H.-H.; Liu, C.-H.; Ou, W.-T.; Huang, K.-H.; Yang, C.-J.; Cheng, M.-J.; Wu, Y.-T. 1,8-Di(2-ethynylaryl)biphenylenes: Palladium-Catalyzed Intramolecular Cycloisomerization and Subsequent Thermal Rearrangement. *Org. Lett.* **2025**, *27* (46), 12886-12891. https://doi.org/10.1021/acs.orglett.5c04302

13.1.12



Patel, C.; Mies, T.; White, A. J. P.; Parsons, P. J.; Barrett, A. G. M. Biomimetic Syntheses of Amorfrutin C and C-5 Substituted Amorfrutin Analogues. *Eur. J. Org. Chem.* **2021**, *2021* (8), 1258-1265. https://doi.org/10.1002/ejoc.202001487

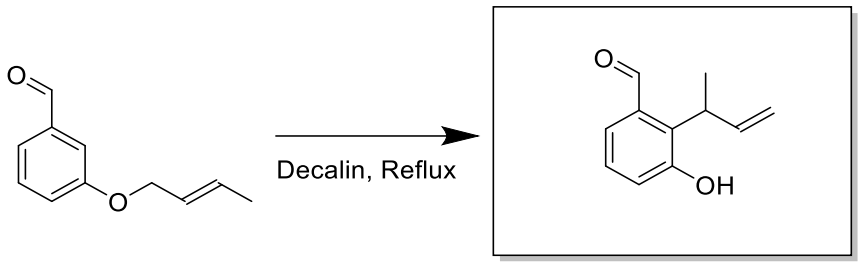
13.1.13



Hint: An intramolecular reaction occurs before the reaction with a reagent.

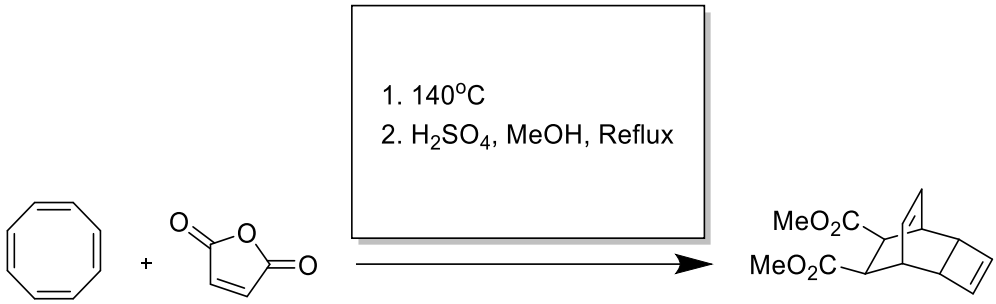
Corti, V.; Barløse, C. L.; Østergaard, N. L.; Kristensen, A.; Jessen, N. I.; Jørgensen, K. A. Organocatalytic Enantioselective Thermal [4 + 4] Cycloadditions. *J. Am. Chem. Soc.* **2023**, *145* (2), 1448-1459. https://doi.org/10.1021/jacs.2c12750

13.1.14



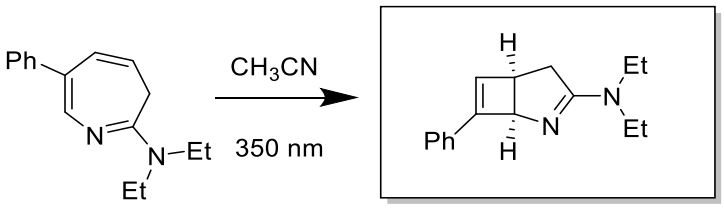
Chang, M.-Y.; Lai, K.-X.; Chen, K.-T. *tert*-BuOOH/Cu(acac)$_2$-Mediated Intramolecular Oxidative Lactonization of *o*-Allyl Arylaldehydes: Synthesis of 1-Oxoisochromans. *Synthesis* **2021**, *53* (3), 527-537. https://doi.org/10.1055/s-0040-1706469

13.1.15



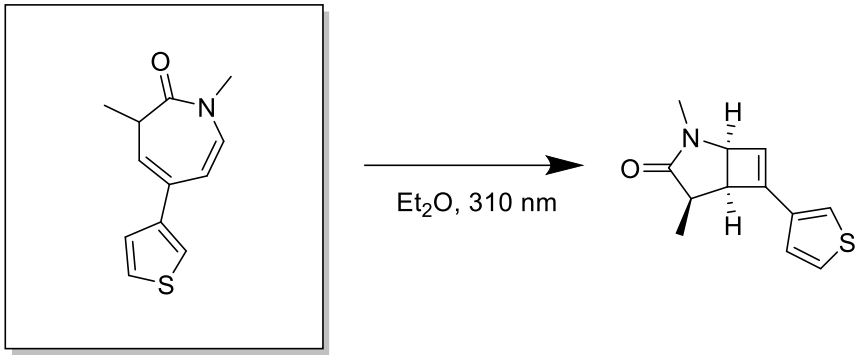
Holl, M. G.; Lambert, T. H. Ring-Opening Carbonyl-Olefin Metathesis of Cyclobutenes. *ACS Catal.* **2022**, *12* (9), 4813-4817. https://doi.org/10.1021/acscatal.2c01188

13.1.16



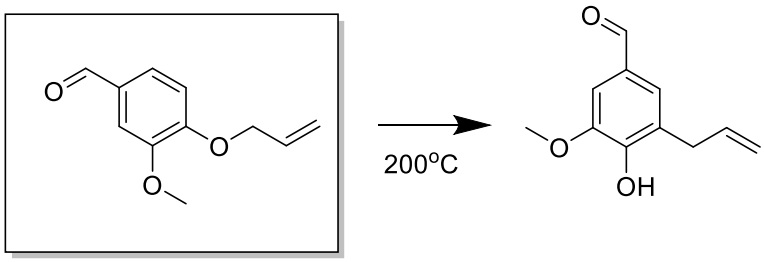
Matador, E.; Tilby, M. J.; Saridakis, I.; Pedrón, M.; Tomczak, D.; Llaveria, J.; Atodiresei, I.; Merino, P.; Ruffoni, A.; Leonori, D. A Photochemical Strategy for the Conversion of Nitroarenes into Rigidified Pyrrolidine Analogues. *J. Am. Chem. Soc.* **2023**, *145* (50), 27810-27820. https://doi.org/10.1021/jacs.3c10863

13.1.17



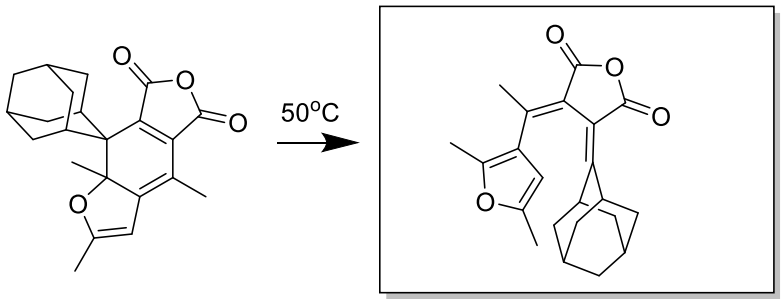
Luo, Y.; Zhou, L.; Qi, X.; Min, C. Divergent Skeletal Editing of Pyridinium Salts to Azepinones and Pyrrolidinones via Formal Carbonyl Insertion. *J. Am. Chem. Soc.* **2026**, *148* (18). https://doi.org/10.1021/jacs.6c03052

13.1.18



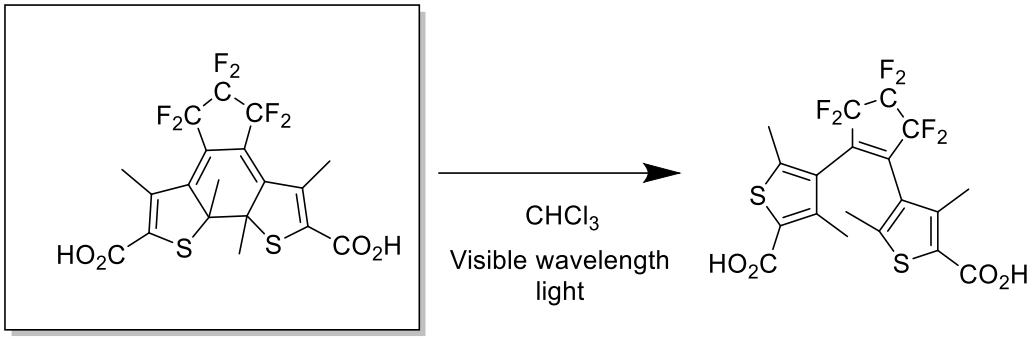
Gao, Z.; Chen, Q.; Xie, H. Atom-Economic Molecular Design of Vanillin-Based Tetraene for Tunable Polyesters via Thiol-Ene Click Polymerization. *Chem. Commun.* **2026**, *62* (29), 7603-7606. https://doi.org/10.1039/D6CC00908E

13.1.19



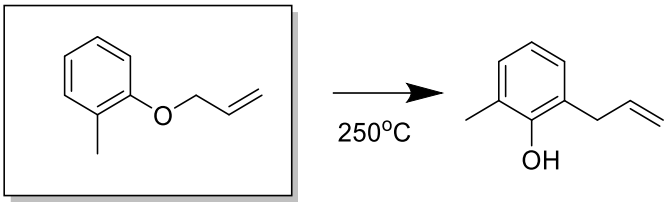
Eichler, C.; Rázková, A.; Müller, F.; Kopacka, H.; Huppertz, H.; Hofer, T. S.; Schwartz, H. A. Paving the Way to the First Functional Fulgide@MOF Hybrid Materials. *Chem. Mater.* **2021**, *33* (10), 3757-3766. https://doi.org/10.1021/acs.chemmater.1c00873

13.1.20



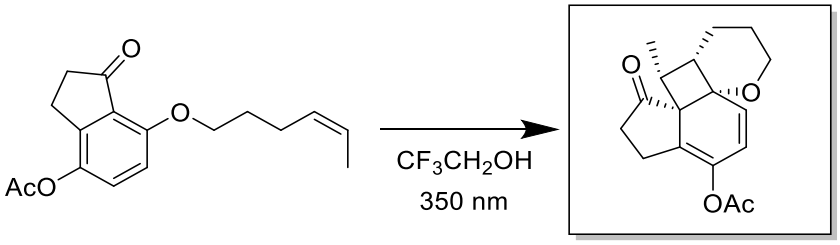
Saeki, Y.; Kayanuma, M.; Nitta, A.; Shigeta, Y.; Kawamura, I.; Nakagawa, T.; Ubukata, T.; Yokoyama, Y. On-Demand Chirality Transfer of Human Serum Albumin to Bis(thiophen-2-yl)hexafluorocyclopentenes through Their Photochromic Ring Closure. *J. Org. Chem.* **2021**, *86* (18), 12549-12558. https://doi.org/10.1021/acs.joc.1c00849

13.1.21



Nagafuchi, M.; Mizumachi, T.; Sato, Y.; Takatsuki, M.; Matsuzaki, T.; Suzuki, T.; Nakayama, A.; Sako, M.; Arisawa, M. Long-Range Isomerisation/Cyclopropane Isomerisation/Cycloisomerisation/Aromatisation Reactions Using Multifunctional Rhodium Catalysts. *Org. Biomol. Chem.* **2026**, *24* (22), 4605-4614. https://doi.org/10.1039/D6OB00534A

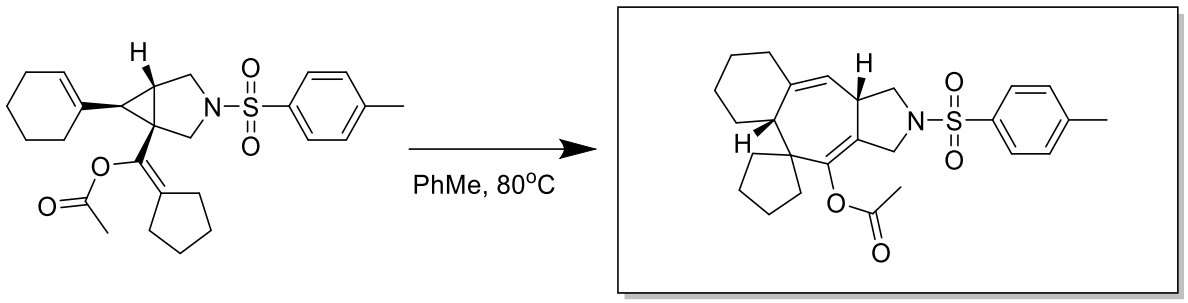
13.1.22



Hint: A four-membered ring is formed.

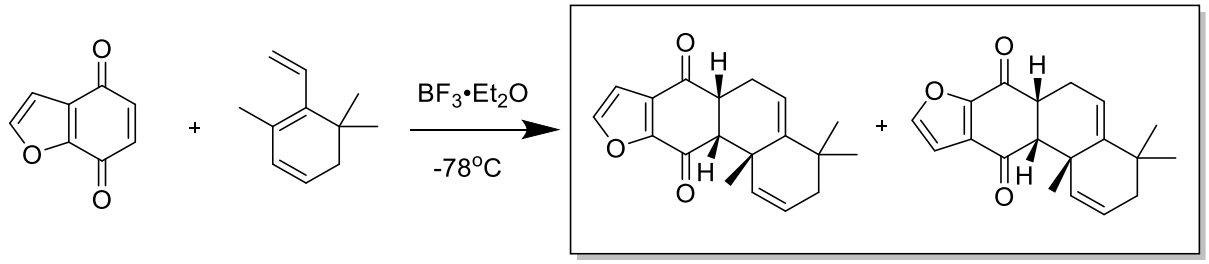
Gilbert, A.; Zuber, J.; Bach, T. Intramolecular *ortho* Photocycloaddition of 4-Substituted 7-(4′-Alkenyloxy)-1-indanones and Ensuing Reaction Cascades. *J. Org. Chem.* **2025**, *90* (11), 4099-4107. https://doi.org/10.1021/acs.joc.5c00171

13.1.23



Rao, W.; Sally; Berry, S. N.; Chan, P. W. H. Gold-Catalyzed Cycloisomerization of 1,6,8-Dienyne Carbonates and Esters to *cis*-Cyclohepta-4,8-diene-Fused Pyrrolidines. *Chem. Eur. J.* **2014**, *20* (41), 13174-13180. https://doi.org/10.1002/chem.201402500

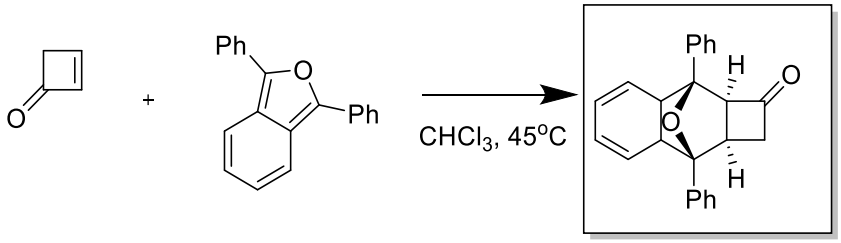
13.1.24



Note: $BF_3 \bullet Et_2O$ is a Lewis acid catalyst used to help favor the production of a particular product. Only two regioisomers are shown in the answer while their stereoisomers are omitted.

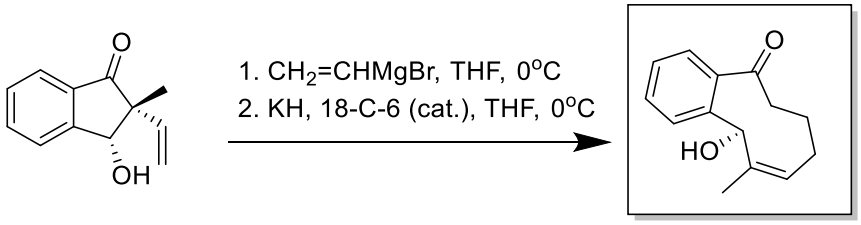
Papidocha, S. M.; Bulthaupt, H. H.; Carreira, E. M. Synthesis of Neocaesalpin A, AA, and Nominal Neocaesalpin K**. *Angew Chem Int Ed* **2023**, *62* (48), e202310149. https://doi.org/10.1002/anie.202310149

13.1.25



Li, X.; Danishefsky, S. J. Cyclobutenone as a Highly Reactive Dienophile: Expanding Upon Diels-Alder Paradigms. *J. Am. Chem. Soc.* **2010**, *132* (32), 11004-11005. https://doi.org/10.1021/ja1056888

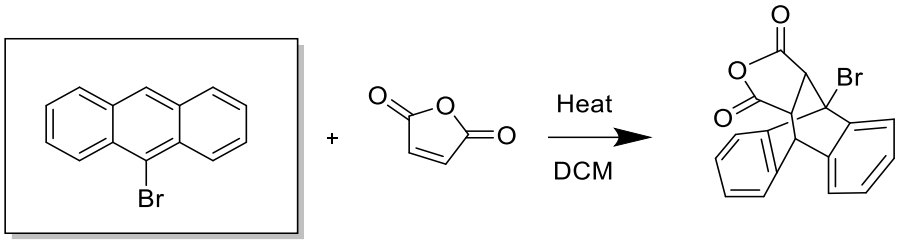
13.1.26



Hint: A nine-membered ring is formed. Learners in introductory organic chemistry can ignore the catalytic role of 18-C-6.

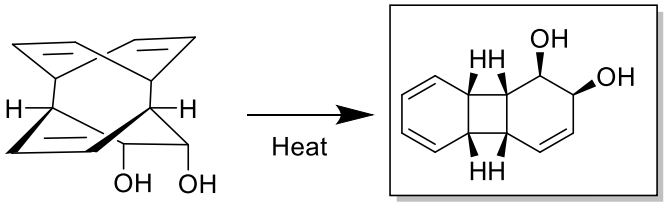
Mondal, A.; Satpathi, B.; Ramasastry, S. S. V. Phosphine-Catalyzed Intramolecular Vinylogous Aldol Reaction of α-Substituted Enones. *Org. Lett.* **2022**, *24* (1), 256-261. https://doi.org/10.1021/acs.orglett.1c03913

13.1.27



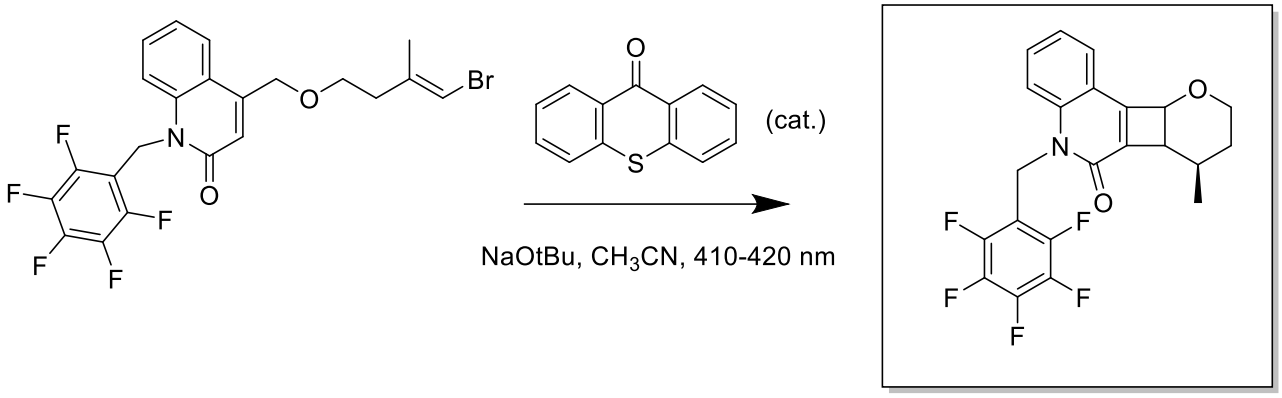
Jadwiszczak, M. J.; Leszczyński, P. J.; Malinowski, P. J. The Role of $AlCl_3$ in Catalysis and Regioselectivity in Diels-Alder Reactions Between Polycyclic Aromatic Hydrocarbons and Maleimides. *Eur. J. Org. Chem.* **2026**, *29* (16), e202501136. https://doi.org/10.1002/ejoc.202501136

13.1.28



Gan, H.; Horner, M. G.; Hrnjez, B. J.; McCormack, T. A.; King, J. L.; Gasyna, Z.; Chen, G.; Gleiter, R.; Yang, N.-C. C. Chemistry of *syn-o,o'*-Dibenzene. *J. Am. Chem. Soc.* **2000**, *122*, 12098-12111. https://doi.org/10.1021/ja0023579

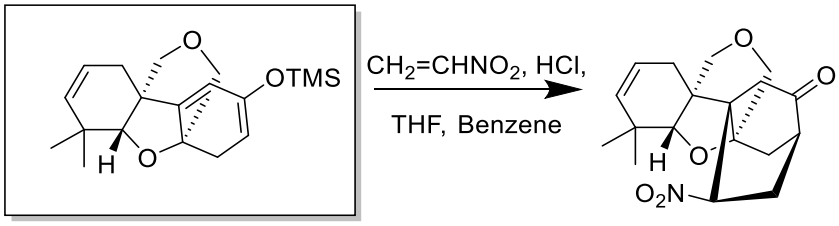
13.1.29



Hint: From the reaction conditions, note that the transformation is performed under basic, photochemical conditions. Learners in introductory organic chemistry do not need to understand the catalytic role of the catalyst in this reaction. The reaction forms a new six-membered ring.

Pan, G.; Qin, S.; Xu, D.; Kühn, F. E.; Guo, H. Visible Light-Induced Pericyclic Cascade Reaction for the Synthesis of Quinolinone Derivatives with an Oxabicyclo[4.2.0]octene Skeleton. *Org. Lett.* **2021**, *23* (8), 2959-2963. https://doi.org/10.1021/acs.orglett.1c00642

13.1.30

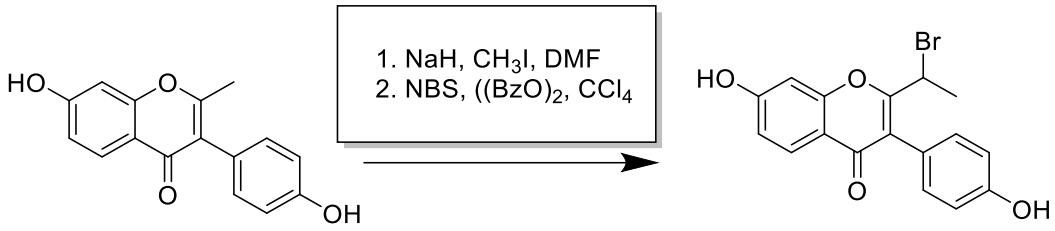


Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. Enantioselective Total Synthesis of (−)-Maoecrystal V. *J. Am. Chem. Soc.* **2014**, *136* (51), 17750-17756. https://doi.org/10.1021/ja5109694

Section 14: Multistep Synthesis 2

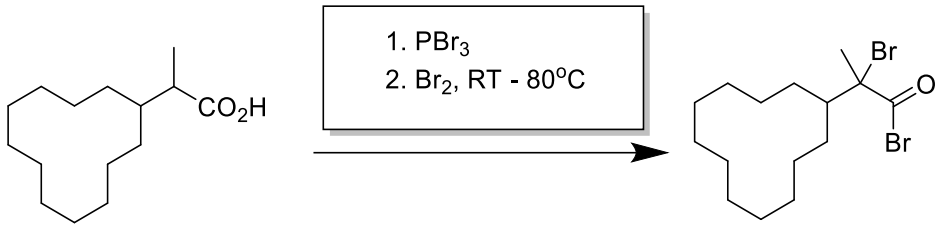
The multistep syntheses presented in this section draw upon fundamental concepts and reactions in all sections. For each of the questions below, provide reagents that would produce the product indicated from the starting material.

14.1



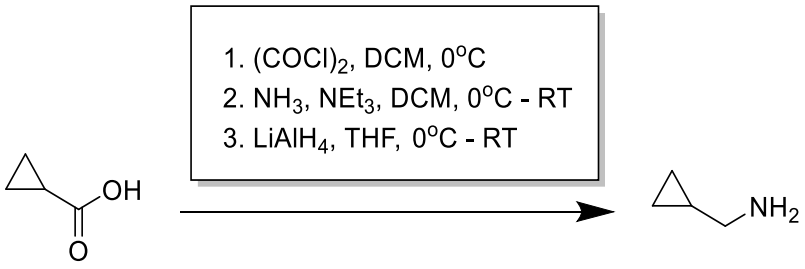
Al-Maharik, N.; Daqqa, M.; AlObaid, A.; Abdallah, L.; Zarrouk, A.; AlAli, A.; Warad, I. Synthesis, XRD/HSA-Interactions, Synthon, TD-DFT/Optical Analysis, Docking and Antibacterial Evaluation of Two (±)-Isoflavonoid Derivatives. *J. Mol. Struct.* **2024**, *1313*, 138700. https://doi.org/10.1016/j.molstruc.2024.138700

14.2



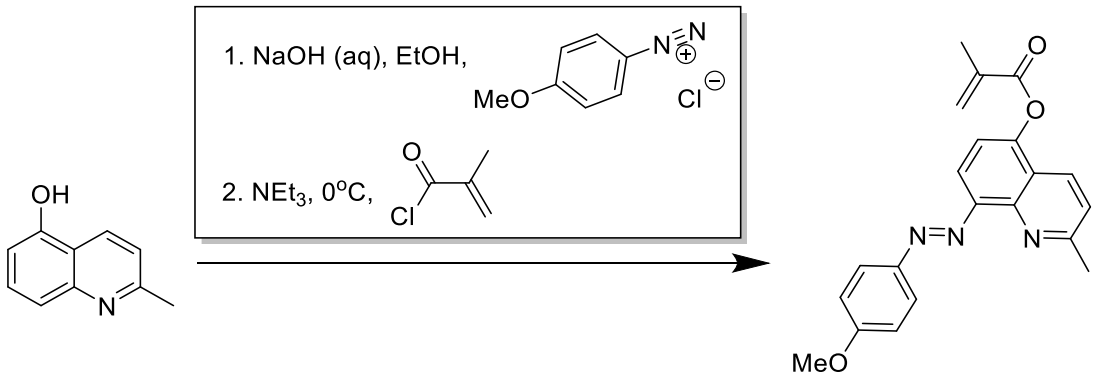
Zhong, F.; Anderson, R. L.; Oyala, P. H.; Fu, G. C. Photoinduced, Copper-Catalyzed Enantioconvergent Azidation of Alkyl Halides. *J. Am. Chem. Soc.* **2025**, *147* (36), 32963–32970. https://doi.org/10.1021/jacs.5c10003

14.3



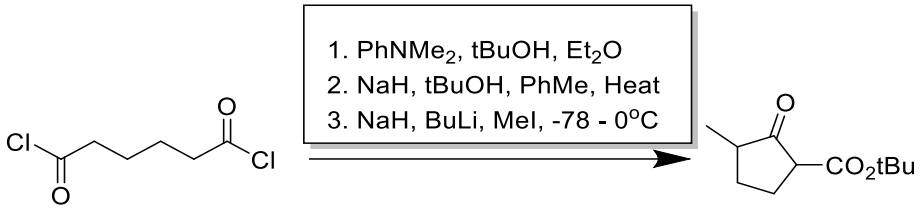
Qi, J.; Wang, C.; Wang, G.; O'Neill, P.; Reddy Dubbaka, S.; Ting Ang, H.; Chen, X.; Wu, J. Strain-Release-Driven Electrochemical Skeletal Rearrangement of Non-Biased Alkyl Cyclopropanes/Butanes. *Angew. Chem. Int. Ed.* **2025**, *64* (1), e202413723. https://doi.org/10.1002/anie.202413723

14.4



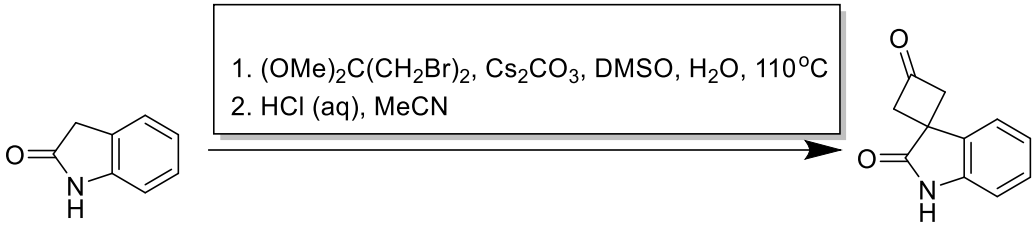
Chomicki, D.; Kharchenko, O.; Kaczmarek-Kędziera, A.; Czaplicki, R.; Krupka, O.; Kowalska, D.; Jahani, S. A.; Smokal, V.; Derkowska-Zielinska, B. Thermal Isomerization Rates of New Azoquinoline-Functionalized Copolymers as a Function of Substitution Patterns. *ChemPhysChem* **2025**, *26* (12), e202401155. https://doi.org/10.1002/cphc.202401155

14.5



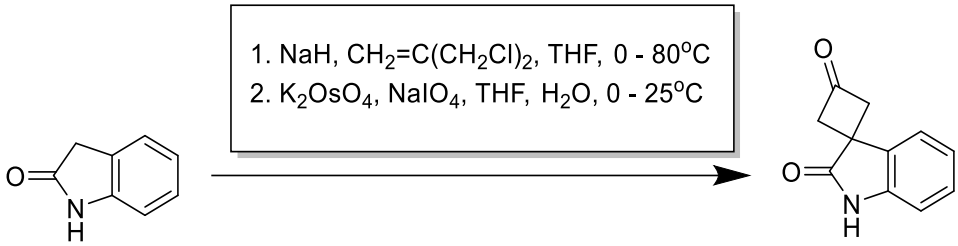
Bunnage, M. E.; Chippindale, A. M.; Davies, S. G.; Parkin, R. M.; Smith, A. D.; Withey, J. M. Asymmetric Synthesis of (1R,2S,3R)-3-Methylcispentacin and (1S,2S,3R)-3-Methyltranspentacin by Kinetic Resolution of *tert*-Butyl (±)-3-Methylcyclopentene-1-carboxylate. *Org. Biomol. Chem.* **2003**, *1* (21), 3698-3707. https://doi.org/10.1039/B306935B

14.6



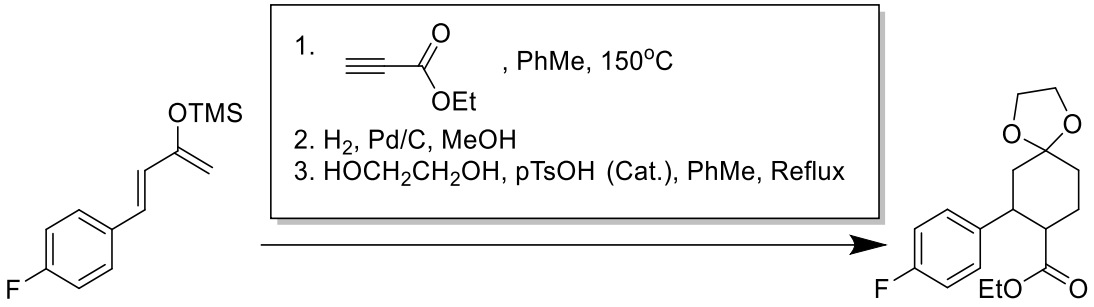
Cao, T. D. C.; Neufeld, K.; Zarate, C.; Nichols, C. J.; Lellek, V.; Deidda, R.; Conza, M.; Schleiss, P.; Rinderhagen, H.; Pye, P.; Muuronen, M.; Chen, W.; Tona, V.; Jouffroy, L.; Viereck, P.; Matcha, K. An Expedient Synthetic Route to the Long-Acting RSV Inhibitor JNJ-6231 via Stereoselective Enzymatic Amination and Regioselective Alkylation. *Org. Process Res. Dev.* **2026**, *30* (1), 121-134. https://doi.org/10.1021/acs.oprd.5c00352

14.7



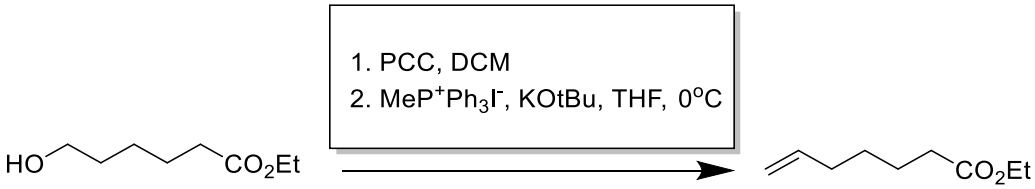
Cao, T. D. C.; Neufeld, K.; Zarate, C.; Nichols, C. J.; Lellek, V.; Deidda, R.; Conza, M.; Schleiss, P.; Rinderhagen, H.; Pye, P.; Muuronen, M.; Chen, W.; Tona, V.; Jouffroy, L.; Viereck, P.; Matcha, K. An Expedient Synthetic Route to the Long-Acting RSV Inhibitor JNJ-6231 via Stereoselective Enzymatic Amination and Regioselective Alkylation. *Org. Process Res. Dev.* **2026**, *30* (1), 121-134. https://doi.org/10.1021/acs.oprd.5c00352

14.8



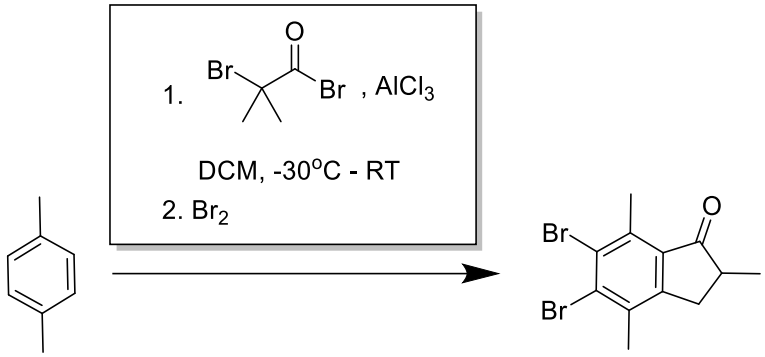
Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in *sp*^{3}-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

14.9



Vulovic, B.; Trmcic, M.; Matovic, R.; Saicic, R. N. Cyclization Reactions of Oxyallyl Cation. A Method for Cyclopentane Ring Formation. *Org. Lett.* **2019**, *21* (23), 9618–9621. https://doi.org/10.1021/acs.orglett.9b03791

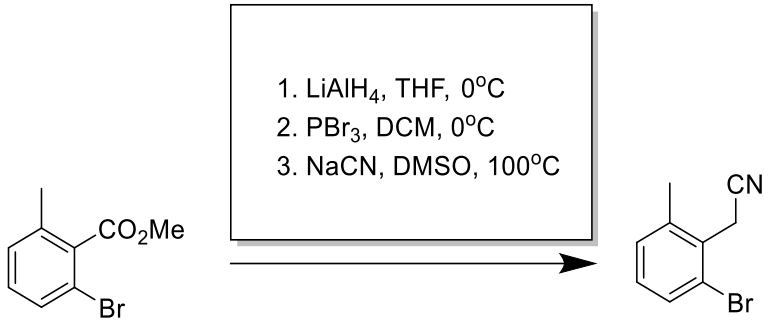
14.10



The authors did not use a Lewis acid in step 2 for the reaction to work.

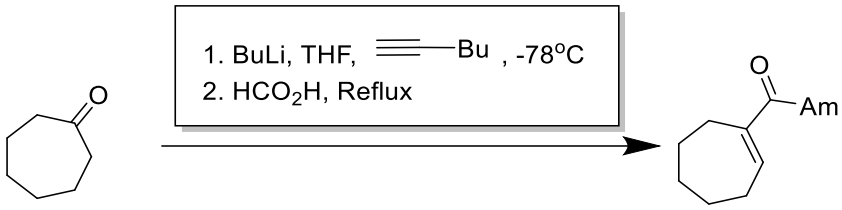
Kulyabin, P. S.; Sharikov, M. I.; Izmer, V. V.; Kononovich, D. S.; Goryunov, G. P.; Alexeev, N. V.; Uborsky, D. V.; Vittoria, A.; Antinucci, G.; Ehm, C.; Budzelaar, P. H. M.; Cipullo, R.; Busico, V.; Voskoboynikov, A. Z. Triptycene as a Scaffold in Metallocene Catalyzed Olefin Polymerization. *Dalton Trans.* **2024**, *53* (22), 9516-9525. https://doi.org/10.1039/D4DT01170H

14.11



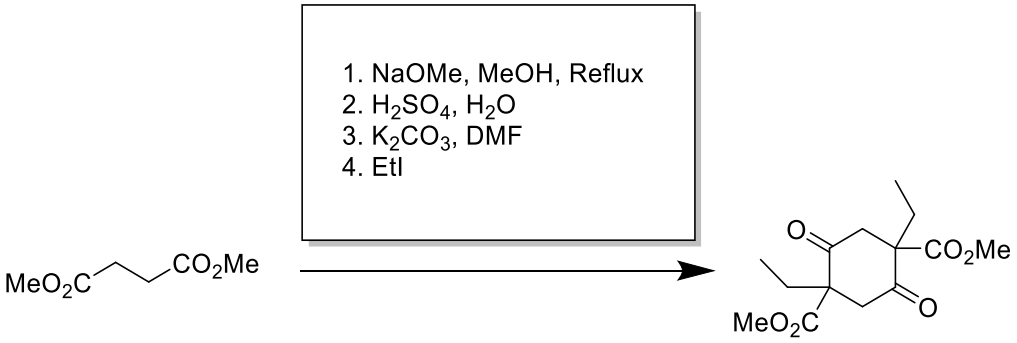
Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in *sp*^{3}-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

14.12



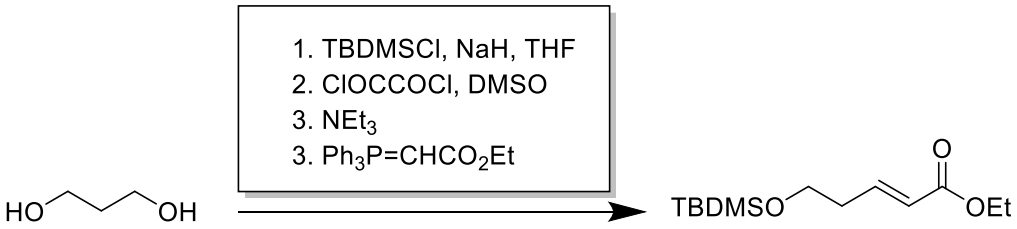
Scarpi, D.; Visi, S.; Muzzu, A.; Occhiato, E. G. One-Pot Gold(I)-Catalyzed Rautenstrauch Rearrangement/Nitrosocarbonyl Hetero-Diels–Alder Reaction Sequence for the Synthesis of α-Hydroxylated Cyclopentenones. *Eur. J. Org. Chem.* **2026**. *29* (27), e70611. https://doi.org/10.1002/ejoc.70611

14.13



Tang, X.; Westlie, A. H.; Watson, E. M.; Chen, E. Y.-X. Stereosequenced Crystalline Polyhydroxyalkanoates from Diastereomeric Monomer Mixtures. *Science* **2019**, *366* (6466), 754-758. https://doi.org/10.1126/science.aax8466

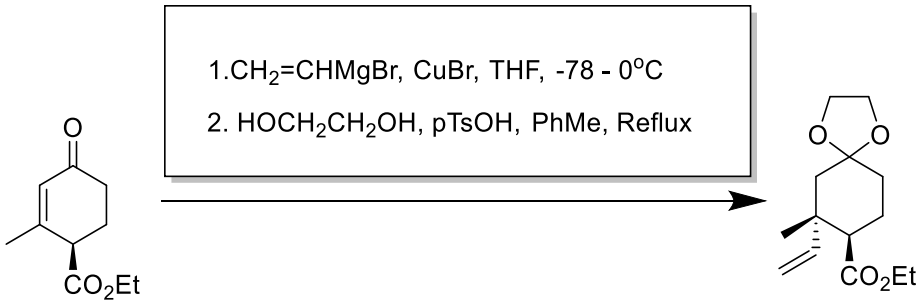
14.14



Step 2 and 3 are Swern oxidation conditions.

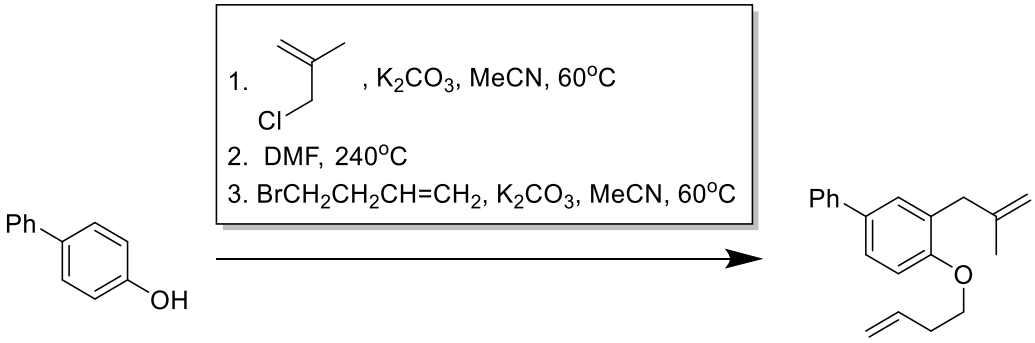
Mortensen, M. S.; Osbourn, J. M.; O'Doherty, G. A. De Novo Formal Synthesis of (−)-Virginiamycin M_2 via the Asymmetric Hydration of Dienoates. *Org. Lett.* **2007**, *9* (16), 3105–3108. https://doi.org/10.1021/ol071145e

14.15



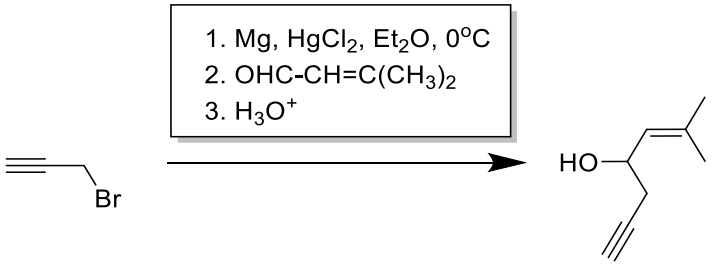
Yue, G.; Yang, L.; Yuan, C.; Du, B.; Liu, B. Total Syntheses of Lindenane-Type Sesquiterpenoids: (±)-Chloranthalactones A, B, F, (±)-9-Hydroxy Heterogorgiolide, and (±)-Shizukanolide E. *Tetrahedron* **2012**, *68* (47), 9624–9637. https://doi.org/10.1016/j.tet.2012.09.053

14.16



Nagafuchi, M.; Mizumachi, T.; Sato, Y.; Takatsuki, M.; Matsuzaki, T.; Suzuki, T.; Nakayama, A.; Sako, M.; Arisawa, M. Long-Range Isomerisation/Cyclopropane Isomerisation/Cycloisomerisation/Aromatisation Reactions Using Multifunctional Rhodium Catalysts. *Org. Biomol. Chem.* **2026**, *24* (22), 4605-4614. https://doi.org/10.1039/D6OB00534A

14.17



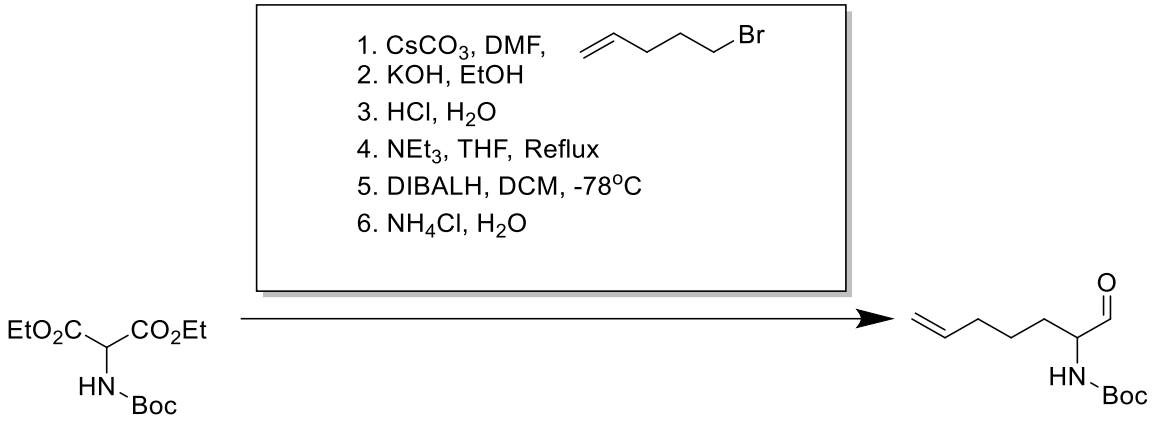
Li, S.; Ma, S. CO_2 -Activation for γ-Butyrolactones and Its Application in the Total Synthesis of (±)-Heteroplexisolide E. *Chem. - Asian J.* **2012**, *7* (10), 2411–2418. https://doi.org/10.1002/asia.201200467

14.18



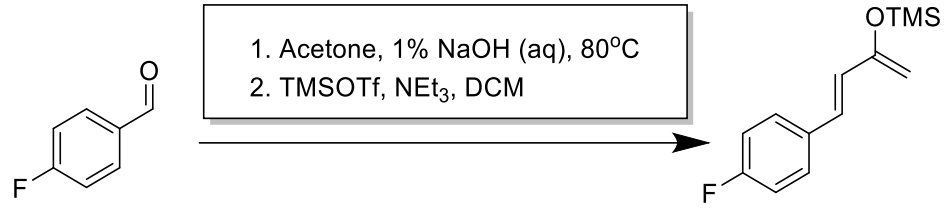
Narayanan, D.; Tran, K. T.; Pallesen, J. S.; Solbak, S. M. Ø.; Qin, Y.; Mukminova, E.; Luchini, M.; Vasilyeva, K. O.; González Chichón, D.; Goutsiou, G.; Poulsen, C.; Haapanen, N.; Popowicz, G. M.; Sattler, M.; Olagnier, D.; Gajhede, M.; Bach, A. Development of Noncovalent Small-Molecule Keap1-Nrf2 Inhibitors by Fragment-Based Drug Discovery. *J. Med. Chem.* **2022**, *65* (21), 14481–14526. https://doi.org/10.1021/acs.jmedchem.2c00830

14.19



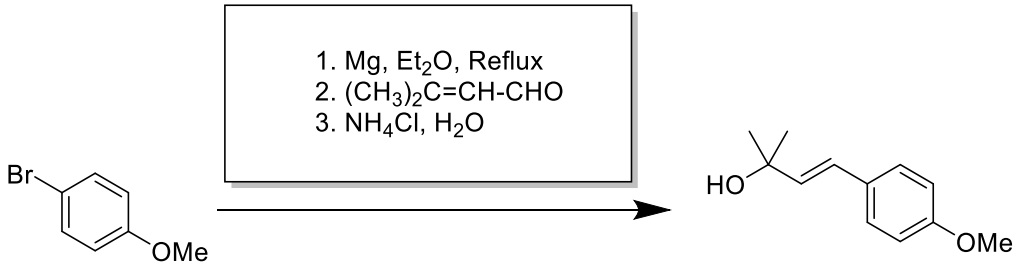
Villela, L. F.; Stoerkler, T.; Labbé, L.; Barriault, L. Bismuth-Catalyzed Photoinduced Ligand-to-Metal Charge Transfer (LMCT) Hydrodecarbonylation of Aldehydes. *Org. Lett.* **2026**, *28* (9), 3057-3062. https://doi.org/10.1021/acs.orglett.6c00395

14.20



Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in sp^3-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

14.21



Tsai, S.; Huang, Y.; Chou, C. Carboxylate-Directed Palladium-Catalyzed Regioselective Mizoroki-Heck Alkenylation of *γ* , *δ* -Unsaturated Carboxylic Acids. *Adv. Synth. Catal.* **2023**, *365* (5), 699–703. https://doi.org/10.1002/adsc.202201317

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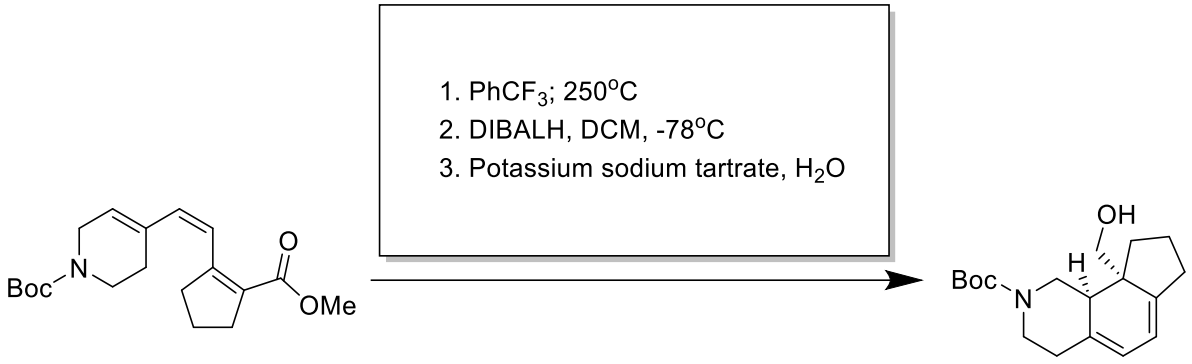
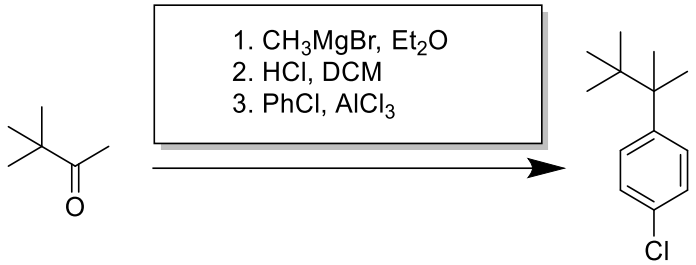


Note: Potassium sodium tartrate is a weak acid.

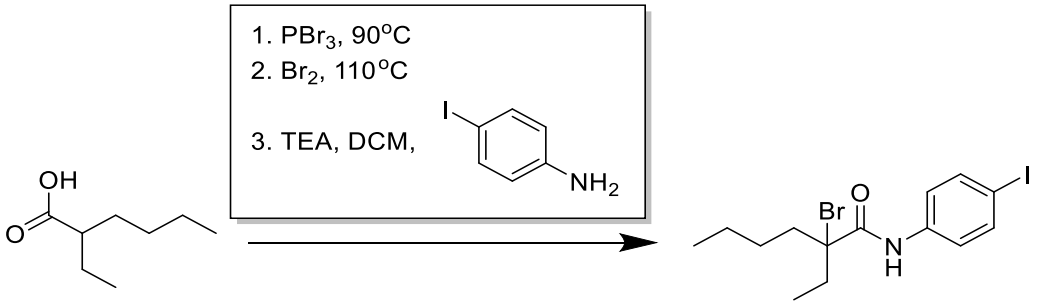
Krieger, J.-P.; Ricci, G.; Lesuisse, D.; Meyer, C.; Cossy, J. Efficient and Modular Synthesis of New Structurally Diverse Functionalized [*n*]Paracyclophanes by a Ring-Distortion Strategy. *Angew. Chem. Int. Ed.* **2014**, *53* (33), 8705-8708. https://doi.org/10.1002/anie.201401070

14.23



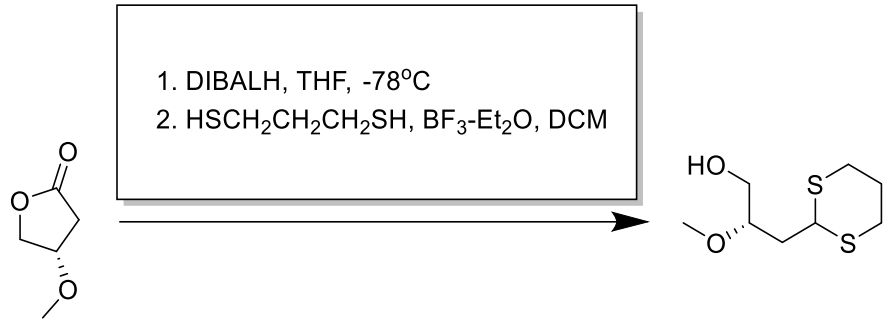
Yang, K.; He, S.; Huang, Y.; Xu, T.; Wang, Y.; Liu, K.; Zhang, L.; Ai, W.; Li, D.; Shen, T. Electrooxidative C-C Fragmentation of Aromatic Radical Cations for Cascade Benzylic Multifunctionalization. *Angew. Chem. Int. Ed.* **2026**, *65* (12), e22498. https://doi.org/10.1002/anie.202522498

14.24



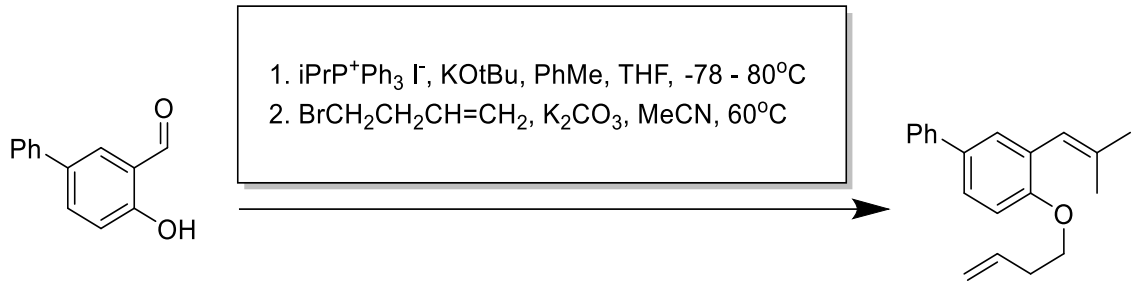
Tsuchiya, N.; Iwashita, I.; Yamamoto, T.; Akagawa, H.; Nishikata, T. Lewis Acid Catalyzed Stereospecific Hydroxylation of Chiral Tertiary Alkyl Halides. *Chem. Lett.* **2024**, *53* (2), upae005. https://doi.org/10.1093/chemle/upae005

14.25



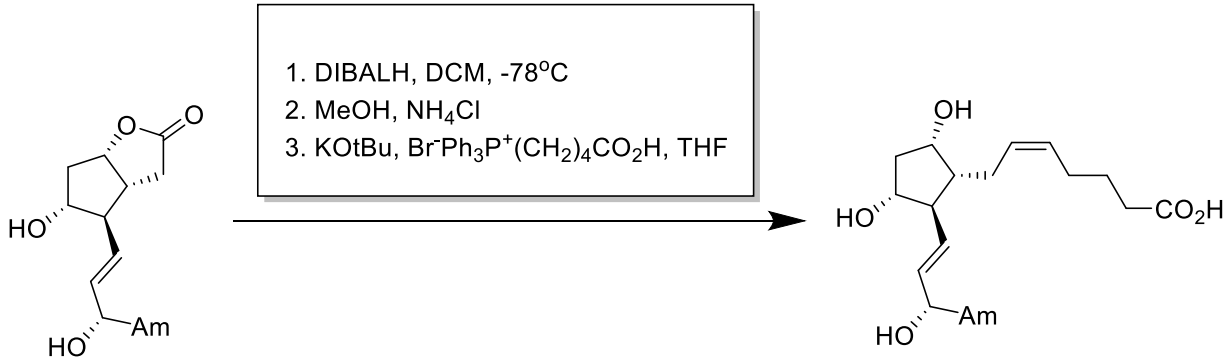
Ghidu, V. P.; Wang, J.; Wu, B.; Liu, Q.; Jacobs, A.; Marnett, L. J.; Sulikowski, G. A. Synthesis and Evaluation of the Cytotoxicity of Apoptolidinones A and D. *J. Org. Chem*. **2008**, *73* (13), 4949–4955. https://doi.org/10.1021/jo800545r

14.26



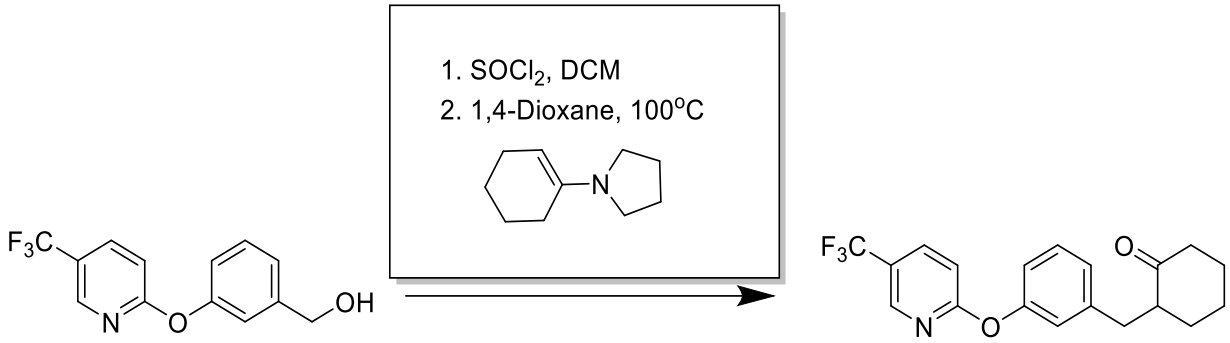
Nagafuchi, M.; Mizumachi, T.; Sato, Y.; Takatsuki, M.; Matsuzaki, T.; Suzuki, T.; Nakayama, A.; Sako, M.; Arisawa, M. Long-Range Isomerisation/Cyclopropane Isomerisation/Cycloisomerisation/Aromatisation Reactions Using Multifunctional Rhodium Catalysts. *Org. Biomol. Chem.* **2026**, *24* (22), 4605-4614. https://doi.org/10.1039/D6OB00534A

14.27



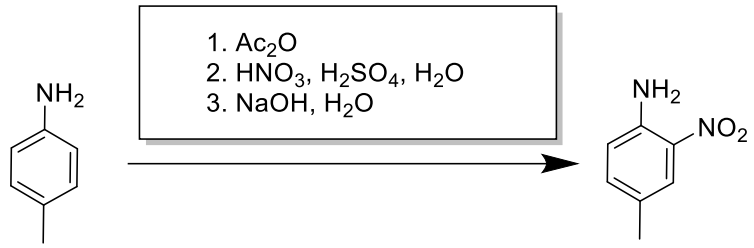
Yin, Y.; Wang, J.; Li, J. A Concise and Scalable Chemoenzymatic Synthesis of Prostaglandins. *Nat. Commun.* **2024**, *15* (1), 2523. https://doi.org/10.1038/s41467-024-46960-y

14.28



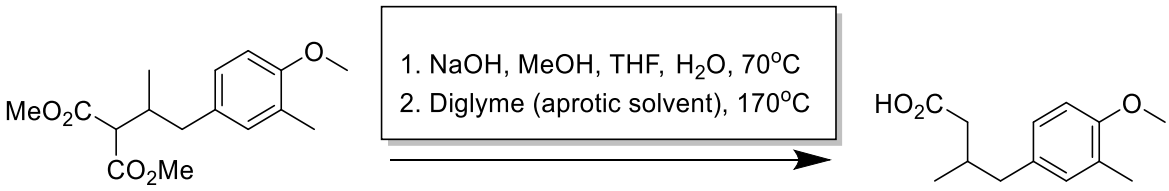
Zhang, Z.; Liang, Z.; Ye, R.; Dong, G. Scanning Nitrogen in *sp*^{3}-Rich Scaffolds Enabled by Carbonyl-to-Nitrogen Atom Swap. *Science* **2026**, *392* (6797), 536-542. https://doi.org/10.1126/science.aef0610

14.29



Glišić, B. Đ.; Hoffmann, M.; Warżajtis, B.; Genčić, M. S.; Blagojević, P. D.; Radulović, N. S.; Rychlewska, U.; Djuran, M. I. Selectivity of the Complexation Reactions of Four Regioisomeric Methylcamphorquinoxaline Ligands with Gold(III): X-Ray, NMR and DFT Investigations. *Polyhedron* **2016**, *105*, 137–149. https://doi.org/10.1016/j.poly.2015.12.009

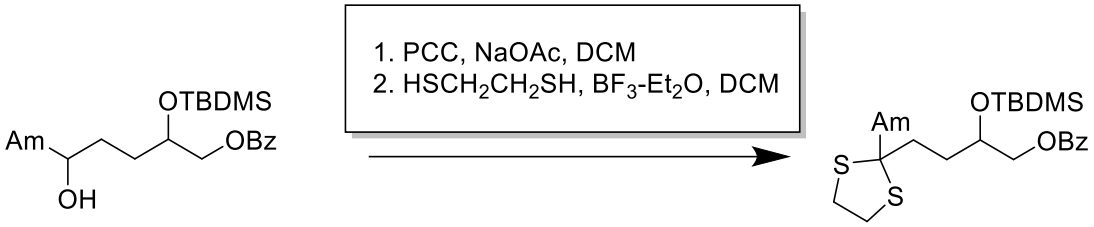
14.30



Note: Diglyme is an aprotic solvent with a high boiling point.

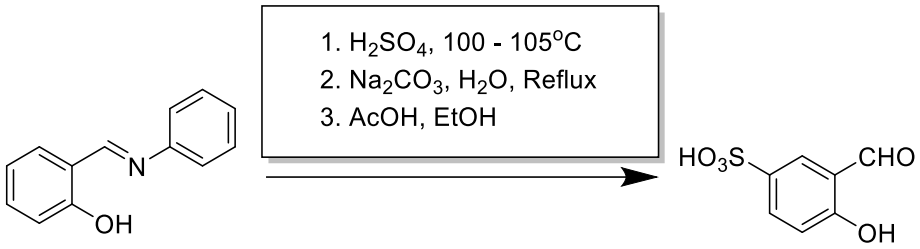
Roosen, P. C.; Karns, A. S.; Ellis, B. D.; Vanderwal, C. D. Evolution of a Short and Stereocontrolled Synthesis of (+)-7,20-Diisocyanoadociane. *J. Org. Chem.* **2022**, *87* (2), 1398–1420. https://doi.org/10.1021/acs.joc.1c02700

14.31



Ferraboschi, P.; Colombo, D.; Compostella, F.; Reza-Elahi, S. Novel Chiral Glycerol Analogues Building Blocks. Application to the Synthesis of Bioactive Glycoglycerolipid Analogues. *Synlett.* **2001**, *2001* (9), 1379–1382. https://doi.org/10.1055/s-2001-16789

14.32



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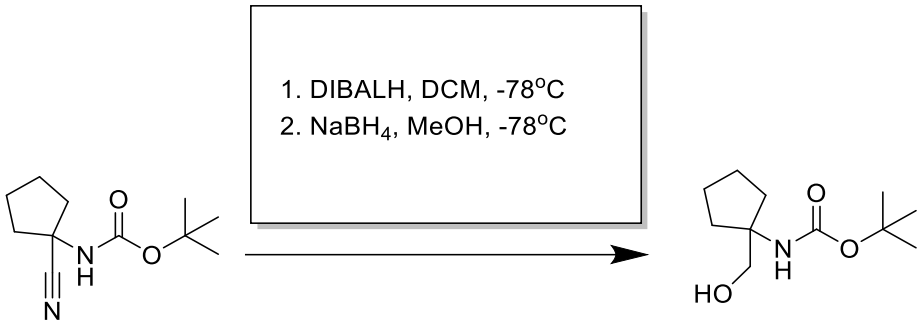
14.33



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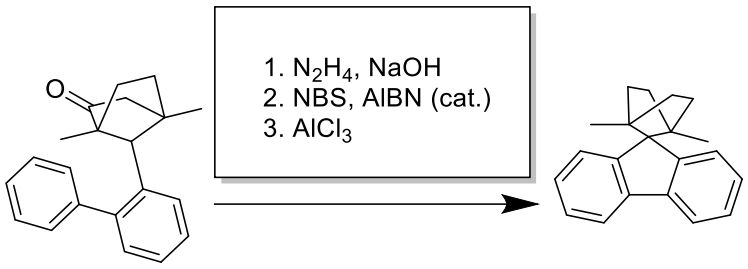
14.34



Note: AIBN reacts with NBS to generate a bromine radical.

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