

# Total Synthesis of Lissodendoric Acid A via Stereospecific Trapping of a Strained Cyclic Allene

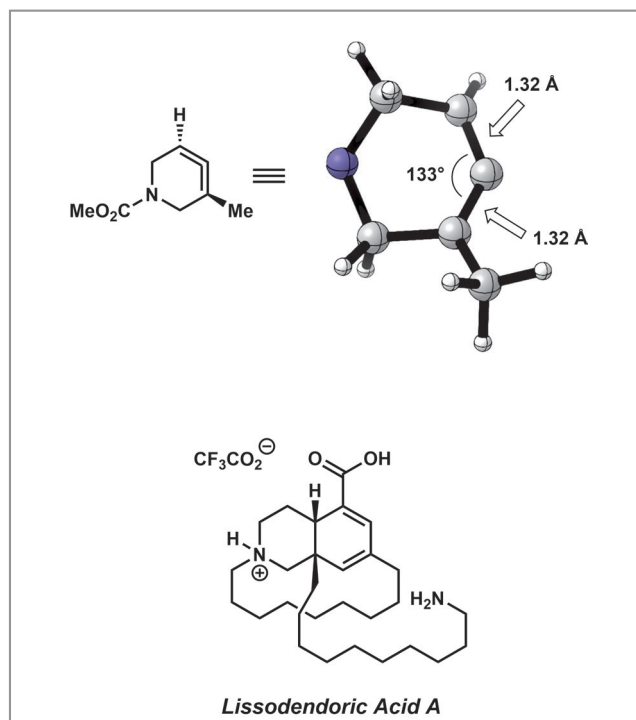
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Over the last decades, it has become apparent that a key priority in the realms of medicinal chemistry and drug discovery was the transition from predominantly aromatic 2D drug candidates (the so called ‘flatlands’) to more complex 3D structures, in order to access novel chemical spaces and – consequently – expanding the structural range of drug candidates. In this context, highly strained and reactive cyclic compounds are increasingly used for accessing complex non-aromatic cyclic structures in stereo- and regio-controlled manner.

Very much influenced by the pharmaceutical community and desires to ‘escape the flatlands’, the laboratory of Professor Neil Garg at UCLA (USA) became interested in non-aromatic strained heterocyclic compounds. “One such scaffold is the strained cyclic allene. This is an interesting scaffold because it had been understudied since its initial discovery in the 1960’s relative to benzyne. The group saw a great opportunity in being able to make nitrogen-containing cyclic allenes,” said Professor Garg, adding: “When I began my career at UCLA, the laboratory was interested in developing strained derivatives of important heterocycles. Early on in my career, we focused on aromatic heterocyclic arynes, like ‘indolynes’ and ‘pyridynes’. This led to several total syntheses and helped establish the synthetic utility of these fleeting unconventional intermediates.”

The laboratory ultimately found that they could make azacyclic allenes and employ them in cycloaddition reactions (reported in *Nat. Chem.* **2018**, *10*, 953–960). “Our initial study was very fundamental and provided insight into how substituents control regioselectivity, as cyclic allenes have two doubles that could potentially react,” explained Professor Garg.

Along with their interest in methodology, the laboratory was simultaneously interested in evaluating azacyclic allenes in total synthesis. “Often, the pursuit of natural product total synthesis reveals gaps in the methodology and drives innovation,” remarked Professor Garg, who continued: “Such is the case as we began to pursue the total synthesis of manzamine alkaloids. We briefly dabbled with a complex natural product called acantholactone, but then one day in 2017, a new manzamine called lissodendoric acid A was reported in the literature. This target made it clear that our azacyclic allene methodology was not perfect for synthetic applications.”



**Figure 1** The strained azacyclic allene, its geometry-optimized structure and the target lissodendoric acid A.

More specifically, the group realized that the regioselectivity needed for the total synthesis was opposite to what was developed in their methodology studies. Professor Garg explained: “Specifically, if one has an alkyl group directly on a cyclic allene double bond, typically cycloaddition (with furan and the like) occurred at the alkene distal to the alkyl substituent. Our total synthesis of lissodendoric acid A would require the opposite sense of selectivity.”

After extensive experimentation, the group found that using pyrones as Diels–Alder partners allowed them to obtain the desired regioselectivity. “We then had a greater problem in having to control absolute stereochemistry,” said Professor Garg. He went on: “What we found, as reported in our recent study, is that we could make a cyclic allene precursor in enantioenriched fashion. To do this, we took advantage of robust CBS-reduction chemistry and coupled it to a general

approach discovered by West and co-workers (*Org. Lett.* **2019**, *21*, 6231–6234). Then, in the key step, we found we could transfer stereochemistry from the cyclic allene precursor, to the cyclic allene, then onto the cycloadduct with a quaternary stereocenter. This allowed us to complete a very short total synthesis, thus establishing that strained cyclic allenes can be used to build very complex structures, including those with multiple stereocenters.”

Professor Garg paid tribute to his co-authors, saying: “A tremendous amount of intellectual and experimental effort went into this study by the remarkable lissodendoric acid A team at UCLA: Francesca Ippoliti, Nathan Adamson, Laura Wonilowicz, Daniel Nasrallah, Evan Darzi, and Joyann Donaldson. Our first-generation total synthesis of the racemic natural product was lengthy. It is incredibly telling that the team had the drive and determination to develop the short and enantio-specific route that was ultimately published.”

Professor Garg concluded: “The important take aways from this study include the importance of teamwork and col-

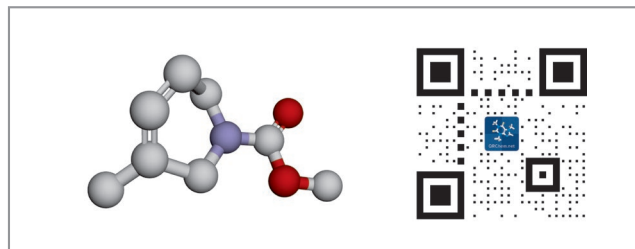
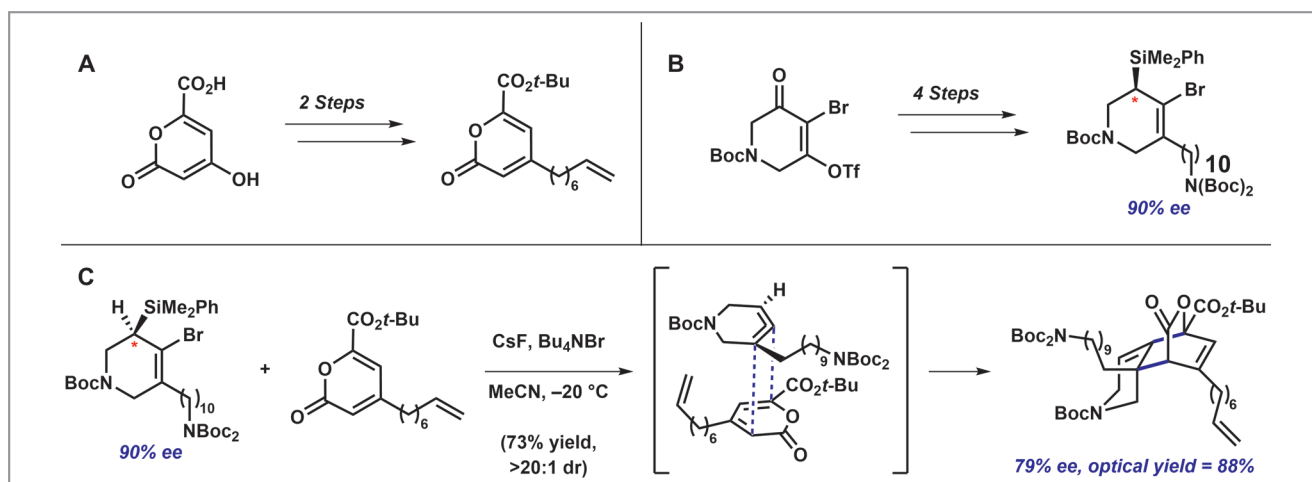


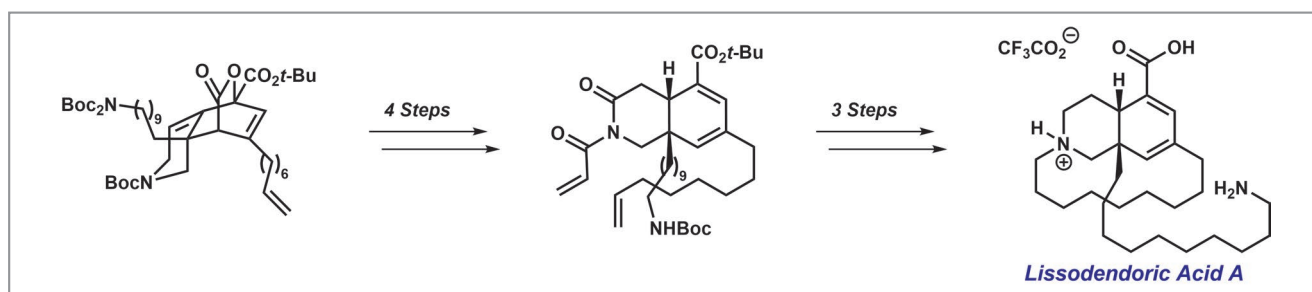
Figure 2 QR Chem code for the strained azacyclic allene.

laboration, innovation, and curiosity. Of course, we hope our total synthesis provides a roadmap to derivatives of lissodendoric acid A, while also enabling the further use of strained cyclic allenes (and related intermediates) in the synthesis of complex structures.”

*Matthew Farber*

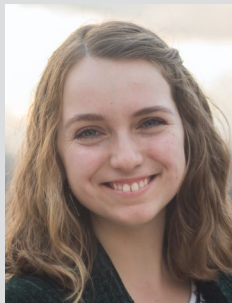


Scheme 1 (A) Synthesis of the pyrone dienophile; (B) Enantioselective route to the silyltriflate cyclic azacyclic allene precursor; (C) Stereo and regio-controlled Diels-Alder cycloaddition of the strained cyclic allene with the pyrone dienophile.



Scheme 2 Completion of the total synthesis of lissodendoric acid A.

## About the authors



Dr. F. Ippoliti

Francesca Ippoliti was born and raised in St. Paul, MN (USA). In 2017, she received her B.S. in chemistry from the University of St. Thomas (USA), where she carried out research under the direction of Professor Lisa E. Prevette. In 2022, she received her Ph.D. in chemistry from the University of California, Los Angeles (USA), where her graduate research focused on total synthesis in the laboratory of Professor Neil K. Garg. She is currently a postdoctoral researcher at the University of Wisconsin–Madison (USA), where she is conducting research on photochemical reactions in the laboratory of Professor Tehshik P. Yoon.



Dr. N. Adamson

Nathan Adamson was born in Greenville, SC (USA) and obtained his B.S. in biochemistry from the College of Charleston (USA) in 2015. He subsequently received his Ph.D. from Duke University (USA) under the supervision of Prof. Steven Malcolmson in 2020. From 2020–2022, Nathan was a Ruth L. Kirschstein postdoctoral fellow in Prof. Neil Garg's group at UCLA (USA). He is currently a scientist in the Discovery Chemistry group at Genentech (USA).



L. Wonilowicz

Laura Wonilowicz was born and raised in Westminster, MD (USA). In 2019, she received her B.S. in biochemistry and a B.A. in chemistry from Virginia Tech (USA), where she carried out research under the direction of Professor Webster L. Santos. She began her graduate studies at the University of California, Los Angeles (USA), where she is currently a fourth-year graduate student in Professor Neil K. Garg's laboratory. Her studies primarily focus on total synthesis and synthetic methods using strained cyclic allenes.



Prof. D. Nasrallah

Daniel Nasrallah was born and raised in Winston-Salem, NC (USA). In 2014, he received his B.S. in chemistry with a concentration in research from the University of North Carolina, Greensboro (USA), where he carried out research under the direction of Professor Mitchell P. Croatt. In 2020, he received his Ph.D. in chemistry from the University of Michigan (USA), where he carried out research under the direction of Professor Corinna S. Schindler. Currently, he is the Donald J. Cram Assistant Adjunct Professor of Chemistry at the University of California, Los Angeles (USA), where he teaches organic chemistry laboratory courses and conducts research in Professor Neil K. Garg's laboratory.



Dr. E. Darzi

Evan Darzi received his B.S. in medicinal biochemistry from Arizona State University in Tempe, AZ (USA), where he performed undergraduate research under Professor Edward Skibo on the synthesis of extended amidines. He received his Ph.D. from the University of Oregon in Eugene, OR (USA), under the guidance of Professor Ramesh Jasti. There he developed syntheses of highly strained [n]cycloparaphenylenes and other 'nanohoops'. He completed his NIH postdoctoral fellowship in Professor Neil K. Garg's laboratory at the University of California, Los Angeles (USA). His postdoctoral studies are focused on the development of strained intermediates in synthetic methodology. Currently, he is the co-founder and CEO of ElectrTect, Inc. a spinout company from Professor Neil Garg's laboratory focused on the development of a marijuana breathalyzer.



Dr. J. Donaldson

Joyann Donaldson was born and raised in Southern California (USA). She received her B.S. in chemistry from Cal Poly Pomona (USA) in 2014. In 2014, she began her doctoral studies at the University of California, Los Angeles (USA) in Professor Neil K. Garg's laboratory where her research primarily focused on harnessing the reactivity of strained intermediates for the construction of heterocycles.

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In 2019, she graduated and moved to San Diego, CA (USA) where she currently works as a medicinal chemist at Pfizer.



*Prof. N. Garg*

**Neil Garg** is the Distinguished Kenneth N. Trueblood Professor of Chemistry at the University of California, Los Angeles (USA). His laboratory develops new synthetic strategies and methodologies to enable the total synthesis of complex bioactive molecules.