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Authors

Hancock, Erin N
Kuker, Erin L
Tantillo, Dean J
et al.

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Lessons in Strain and Stability: An Enantioselective Synthesis of (+)-[5]-Ladderanoic Acid

Erin N. Hancock[a], **Erin L. Kuker**[a], **Dean J. Tantillo**[b], **M. Kevin Brown**[a]

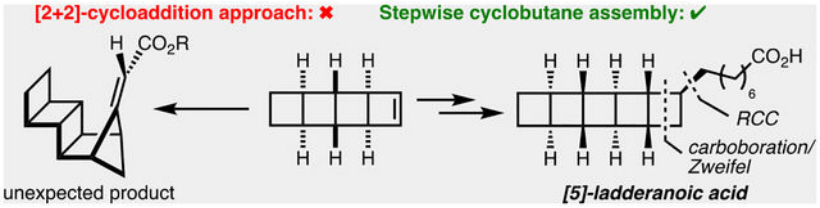
[a]Department of Chemistry, Indiana University, 800 E. Kirkwood Ave. Bloomington, IN 47401

[b]Department of Chemistry, University of California Davis, 1 Shields Ave. Davis, CA 95616

Abstract

The synthesis of structurally complex and highly strained natural products provides unique challenges and unexpected opportunities for the development of new reactions and strategies. Herein, the synthesis of (+)-[5]-ladderanoic acid is reported. *En route* to the target, unusual and unexpected strain-release driven transformations were uncovered. This required a drastic revision of the synthetic design that ultimately led to the development of a novel stepwise cyclobutane assembly by allylboration/Zweifel olefination.

Graphical Abstract



Introduction

Synthesis of structurally complex natural products continues to be an inspiration for the development of new methods and strategies. At times, the unusual positioning of substituents or strained ring systems often reveals unexpected reactivity *en route* to the target.

The ladderane family of natural products is a unique class of molecules that is characterized by a series of fused cyclobutanes.[1,2] Due to their complex structure and unknown biological function,[3] several groups have developed routes to these molecules (Scheme 1). In 2006, Corey reported a synthesis of (+)-[5]-ladderanoic acid (**2**), which featured a diastereoselective photochemical [2+2]-cycloaddition.[4] Ten years later, Burns reported elegant syntheses of (−)-[5]-ladderanoic acid (**2**), (+)-[3]-ladderanol (**1**), and the fully assembled phospholipid **3**.[5] The approach towards (−)-[5]-ladderanoic acid (**2**) featured a Mn-catalyzed C-H chlorination and a desymmertization by an enantioselective Cu-catalyzed

Prof. M. Kevin Brown, brownmkb@indiana.edu.

protoboration. In the case of (+)-[3]-ladderanol (**1**), a diastereoselective [2+2]-cycloaddition established the core structure.

Due to our group's long-standing interest in the chemistry surrounding cyclobutanes, we recently reported a synthesis of (−)-[3]-ladderanol (**1**).[6] The route featured an intramolecular stereoselective [2+2]-cycloaddition between a chiral allenic ketone and an alkene to gain access to the [4.2.0]-bicyclooctane core. In this report, we disclose a synthesis of (+)-[5]-ladderanoic acid (**2**), the unexpected challenges we encountered as a result of working with ladderanes, and highlight the novel solutions we utilized to address them.

Results and Discussion

Our initial strategy for the synthesis of (+)-[5]-ladderanoic acid hinged on a late-stage enantioselective [2+2]-cycloaddition between [4]-ladderene **4** and an allenoate to assemble the final cyclobutane (Scheme 2A). Conversion of the cycloadduct to the target was envisioned to occur through a chain elongation sequence. Inspiration for the proposed [2+2]-cycloaddition stemmed from early work in our lab on related cycloadditions.[7] In these reactions, a wide variety of alkenes, such as cyclopentene (**5**), could be converted to the products through [2+2]-cycloaddition promoted by oxazaborolidine catalysts (*e.g.*, **8**) with good levels of enantioselectivity (Scheme 2B).

An initial strategy towards [4]-ladderene is illustrated in Scheme 3A. In this route, a cycloaddition between [3]-ladderene ester **9** and 1,2-dichloroethylene would give rise to the [4]-ladderane **10**.[8] This product could be elaborated to [4]-ladderene **4** by a sequence involving decarboxylation and dechlorination.

The requisite [3]-ladderene ester **9** was prepared by oxidation of known [3]-ladderane ester **11** (Scheme 3B).4[a] Irradiation of **9** and 1,2-dichloroethylene with UVA (λ_{max} = 350 nm) or UVB (λ_{max} = 313 nm) failed to promote conversion of the starting materials. However, use of UVC (λ_{max} = 254 nm) allowed for consumption of [3]-ladderene ester **9**. Unfortunately, the expected cycloadduct **10** was not detected, but rather a remarkable conversion to ethylene (**13**) and methyl benzoate (**12)** was observed.[9] This highly unusual reaction likely occured by rearrangement of the excited state intermediate **14** to diene **15** (formal retro-4π-electrocyclization), followed by a second rearrangement of the excited state intermediate **16** (formal retro-[2+2]-cycloaddition). At this stage, the intermediacy of diene **15** cannot be confirmed as **14** may undergo direct transformation to **16** without relaxation to the ground state.

An alternative strategy was developed to access [4]-ladderene through implementation of [2+2]-cycloaddition with cyclopentenone and subsequent ring contraction by Wolff rearrangement. Design of this strategy was influenced by the proclivity of photochemical [2+2]-cycloadditions to use cyclopentenone[10] and prior studies from Corey and our lab in the synthesis of related structures.4,6 As such, the synthesis commenced with cycloaddition between cyclopentenone (**17**) and 1,2-dichloroethylene to generate [3.2.0]-bicycloheptane **18** (Scheme 4). Ketal formation and reduction of the dichloride resulted in cyclobutene **19**. A second photochemical [2+2]-cycloaddition with cyclopentenone gave rise to **20** as an

inconsequential mixture of regioisomers. Diazo-formation and subsequent Wolff rearrangement ultimately provided carboxylic acid **21**. Decarboxylation followed by a similar series of transformations provided access to [4]-ladderane carboxylic acid **23**. Conversion of the carboxylic acid to the bromide followed by elimination allowed for synthesis of [4]-ladderene **4**.

With synthesis of [4]-ladderene **4** completed, the key enantioselective cycloaddition with allenoate **24** was explored (Scheme 5). Initial investigations revealed that a productive reaction occurred to generate what was originally thought to be the desired [5]-ladderane **26** with good yield and enantioselectivity when oxazaborolidene **25** was used. However, upon rigorous structural determination by X-ray crystallography of a derivative (**30**), it was revealed that [2.1.1]-bicycle **27** was formed as the exclusive product![11,12] This remarkable transformation is proposed to occur by initial [2+2]-cycloaddition to generate the desired cycloadduct **26** as outlined in Scheme 5. However, due to the inherent ring strain, a retro-[2+2]-cycloaddition occurs rapidly to generate chiral allenoate **28**. Upon C-C bond rotation and crossed-[2+2]-cycloaddition (via **29**), the observed product **27** could be formed. Density functional theory (DFT) calculations (ωB97X-D/6–311+G(d,p); see SI for details) revealed that the [2.1.1]-bicycle **27** is 8 kcal/mol lower in energy that the [2.2.0]-bicycle **26** While the process shown in Scheme 5 has not been reported to the best of our knowledge, a related ketene-alkene [2+2]/retro-[2+2] cycloaddition has been disclosed.[13]

Two additional points regarding this reaction are important to note: (1) When the reaction is monitored by ^{1}H NMR (500 MHz), no intermediates that would correspond to **26** or **28** are detected. This suggests that the initial [2+2] is rate determining followed by rapid subsequent steps. (2) The process is not limited to [4]-ladderene **4**, as reaction of cyclobutene (**31**) was also found to generate the analogous [2.1.1]-bicyclic product **33** and **34** (Scheme 6).[14] This reaction likely proceeds via chiral allenoate **36**. It is interesting that **33** (and likely **34** by analogy) were found epimeric when compared to **27**. One possible explanation for the observed epimeric relationship of **27** and **33** could potentially arise from a change in *E/Z*-selectivity between the initial [2+2]-cyloaddition of [4]-ladderene and cyclobutene. While the basis of this remains unclear, alkene-allenoate [2+2]-cycloaddition have been reported with varrying degrees of *E/Z* selectivities.[7]

To further probe the proposed mechanism, intermediate **36** was independently prepared. Subjection of **36** to the reaction conditions generated the [2.1.1]-bicyclic product **34**. This supports the hypothesis that **36** could be an intermediate in the conversion of cyclobutene and allenoates **24** and **32** to products **33** and **34**, respectively. This product is formed in 50:50 er because the prepared allenoate is also racemic.

Due to the unusual nature of the pericyclic cascade, several other allenoates were evaluated in the transformation (Scheme 7). Reaction with γ-substituted allenoates **38** and **39** led to the expected [2.1.1]-bicyclic products **40** and **41** with high levels of diastereoselectivity. The reaction likely proceeds in an analogous manner to that of the unsubstituted allenoate. To rationalize the formation of the observed diasteromer, [2+2]-cycloaddition must occur to generate diasteromer **42** in which the R-group is located on the concave face of the [2.2.0]-

bicycle. Finally, while $EtAlCl_2$ was found to the optimal promoter, the catalyst **25** was also competent yet give rise to several unidentified byproducts.[15]

Reaction with γ,γ-dimethylsubstituted allenoate **45** and cyclobutene did not give rise to the expected [2.1.1]-bicyclic product but rather cyclopentene **46** (Scheme 7B). To account for the formation of **46** it is proposed that the initial sequence of [2+2]/retro[2+2] occurred to generate **47**. However, at this stage, the crossed-[2+2] is disfavored due to steric considerations of a 4-membered ring transition state relative to a six-membered ring transition state necessary for the ene-reaction (*via* **48**). The product was generated in 79:21 er (absolute stereochemistry is unknown) likely a result of a less selective [2+2]-cycloaddition compared to the unsubstituted allenoate.

At this stage, several photochemical [2+2]-cycloaddition strategies were investigated to elaborate [4]-ladderene **4** to the natural product. One of the major challenges that we experienced was the fact that photochemical [2+2]-cycloadditions typically require cyclic electron deficient alkenes to be one of the reactants. This greatly narrows the type of products that can be generated and as a result, multiple steps to manipulate functional groups *en route* to the target would be incurred.

A specific example that highlights the aforementioned challenges is shown in Scheme 8. We found that the [4]-ladderene could undergo cycloaddition with **49** to install the final cyclobutane ring (product **50**).[16] However, elaboration of this compound to the target proved challenging, mainly due to ring-opening that resulted from attempts to remove the oxygen atom bound to the cyclobutane.[17]

Conscious of the aforementioned problems, we elected to drastically change the approach by dispensing with the notion that a [2+2]-cycloaddition would be the best strategy to install the final cyclobutane. Due to our group's interest in arylboration reactions of alkenes,[18] we devised a 2nd generation strategy that would involve allylboration (**4** to **51**) followed by Zweifel olefination (**51** to **54**) (Scheme 9). Inspiring studies from Hoveyda[19] and Yun[20] on Cu-catalyzed enantioselective allylboration of styrenyl derivatives and borylcupration of cyclobutenes from Tortosa[21] and Burns5 suggested that **51** could be prepared by the merging these two methods (Scheme 9). While Zweifel olefenation is well established in intermolecular variants,[22,23] intramolecular reactions are rare. In only one example, Aggarwal reported the formation of a cyclobutane formed by Zweifel olefination.[24] Upon completion of the allylboration/Zweifel olefination sequence, it was envisioned that the [5]-methylene ladderane **54** could be elaborated to the target through various approaches.

The strategy outlined in Scheme 9 has been implemented to generate (+)-[5]-ladderanonic acid (**2**), as illustrated in Scheme 10. Initially, Cu-catalyzed allylboration was examined with an allyl electrophile that incorporated a vinyl bromide. However, these reactions failed to deliver the desired product in an appreciable yield. Therefore, a vinylsilane was used as a surrogate that not only allowed the allylboration to proceed with good yield and enantioselectivity, but could be elaborated to the vinylbromide **55** by treatment with Br_2 followed by TBAF. Addition of *t*-BuLi to vinyl bromide **55** resulted in generation of borate

52 which underwent reaction smoothly with I_2 to generate [5]-methylene ladderene **54** after 1,2-elimination (via **53**).

[5]-methylene ladderane **54** could be elaborated to (+)-[5]-ladderanonic acid (**2**) through one of two routes (Scheme 10). The first involved a hydroboration-oxidation with 9-BBN followed by Swern oxidation to aldehyde **57**. Intermediate **57** can be converted to (+)-[5]-ladderanoic acid (**2**) though a sequence of epimerization, Wittig olefination, and diimide reduction as demonstrated by Corey.4[a] Alternatively, we elected to explore an approach that would take advantage of an emerging set of reactions introduced by Baran, specifically decarboxylative alkyl-alkyl cross coupling.[25] In this approach, **54** was converted to carboxylic acid **56** through a hydroboration-oxidation sequence. Synthesis of the redox active ester, subsequent Ni-catalyzed cross coupling with dialkylzinc reagent **58**, and hydrolysis provided (+)-[5]-ladderanonic acid (**2**) in 38% yield over 2 steps.[26] It is interesting to note that the Ni-stabilized cyclobutyl radical **59**, or related cylobutyl free radicals generated in the decarboxylative transformation **21** to **22** and **23** to **4** do not undergo strain release promoted ring-opening.[27] DFT calculations (ωB97X-D/6–311+G(d,p); see SI for details) reveal that the free radical of **60** (no Ni) is 27 kcal/mol lower in energy than the free radical of **59** (no Ni). In addition, the predicted barrier for conversion of the free radical of **59** to **60** is only 18 kcal/mol. This suggests that bimolecular capture of the cyclobutyl free radicals is rapid.

Conclusion

In summary, an evolution of a strategy to prepare (+)-[5]-ladderanoic acid is presented. Only through synthesis of this complex natural product did we uncover unusual strain-release promoted transformations that forced a significant change of strategy. The evolution from realizing that a [2+2]-cycloaddition approach was not viable led to development of a novel stepwise installation of the final cyclobutane through an allylboration/Zweifel olefination sequence. In addition, we have uncovered a novel process for the synthesis of [2.1.1]-bicycles from unlikely precursors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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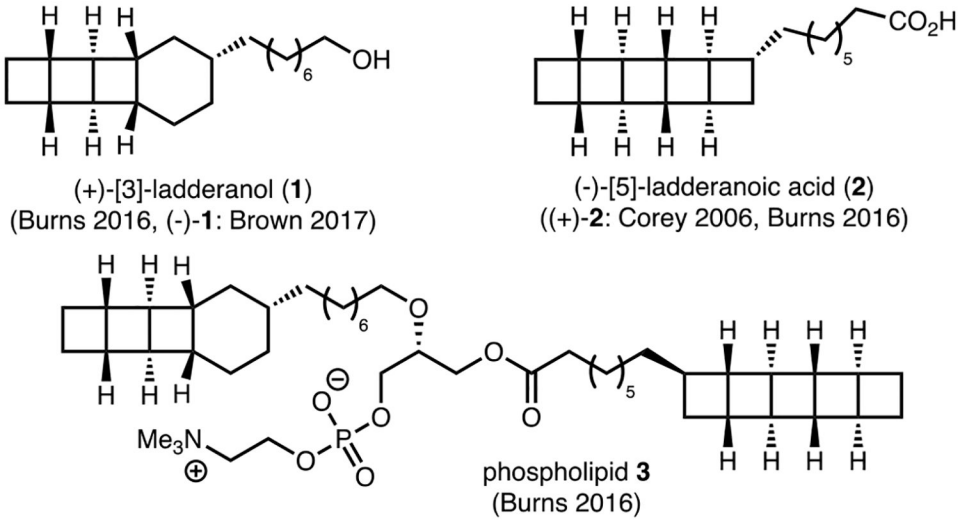
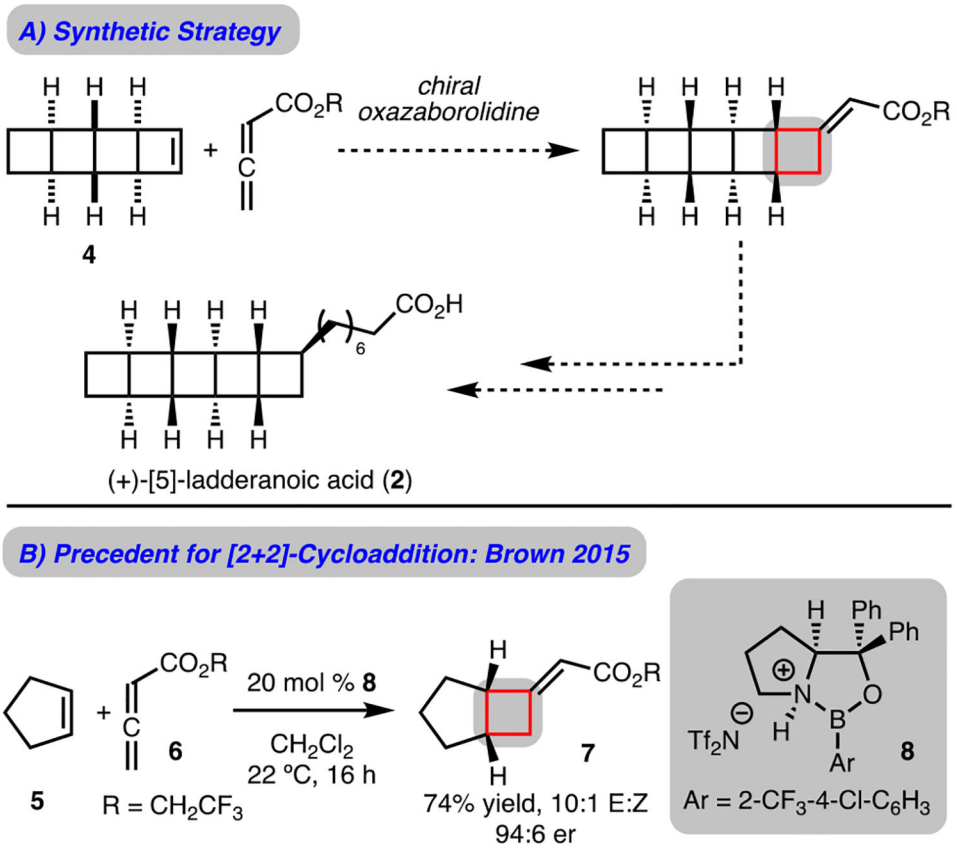
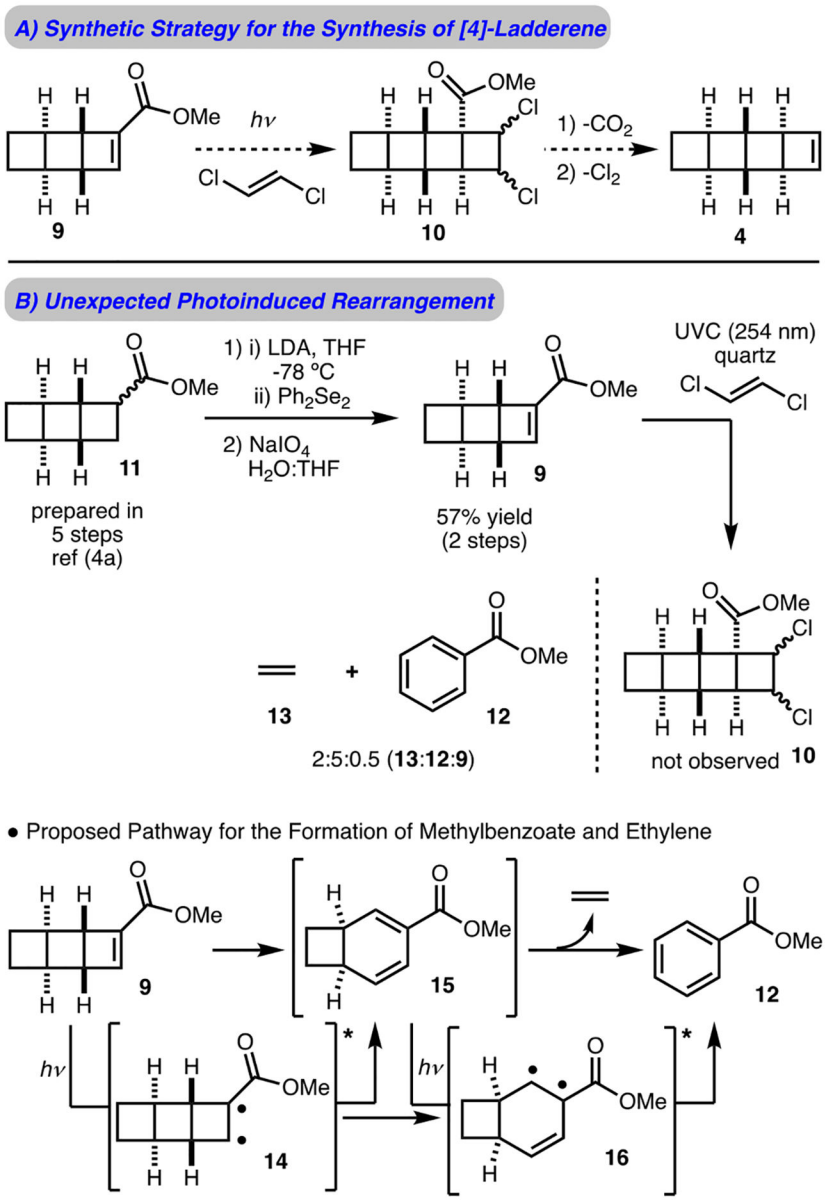


Scheme 1.
Prior Syntheses of Ladderanes

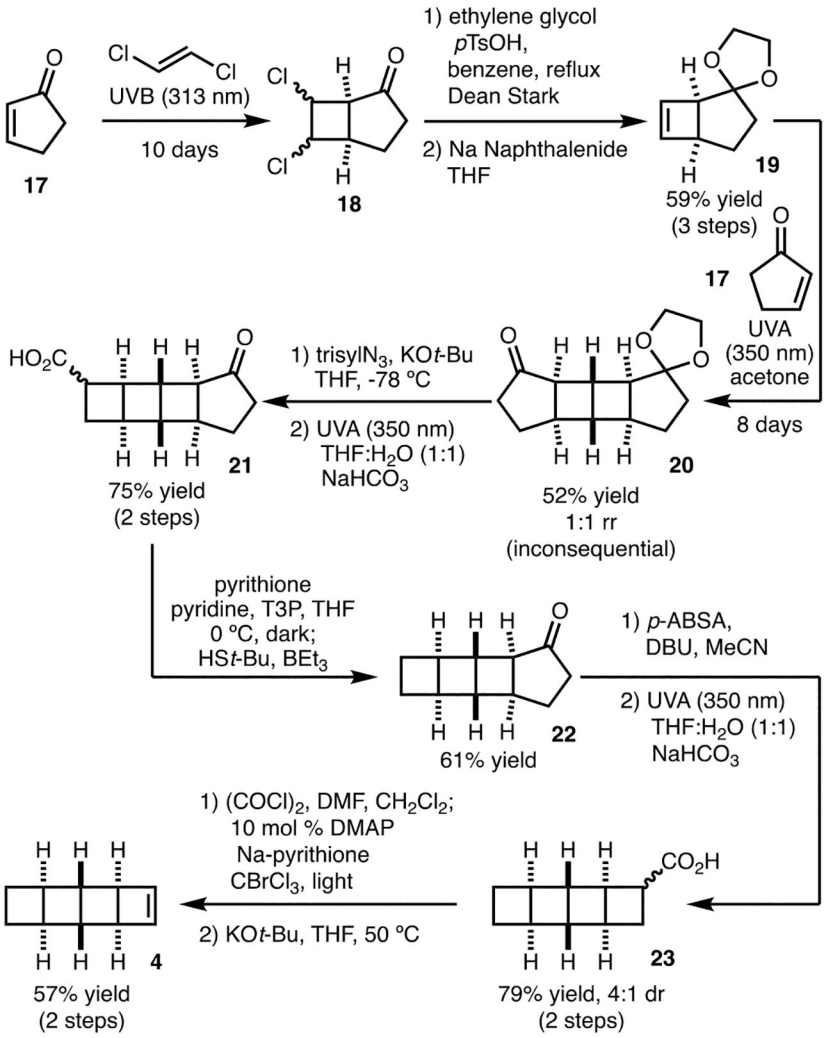


Scheme 2.
Strategy for the Synthesis of (+)-[5]-Ladderanoic Acid.



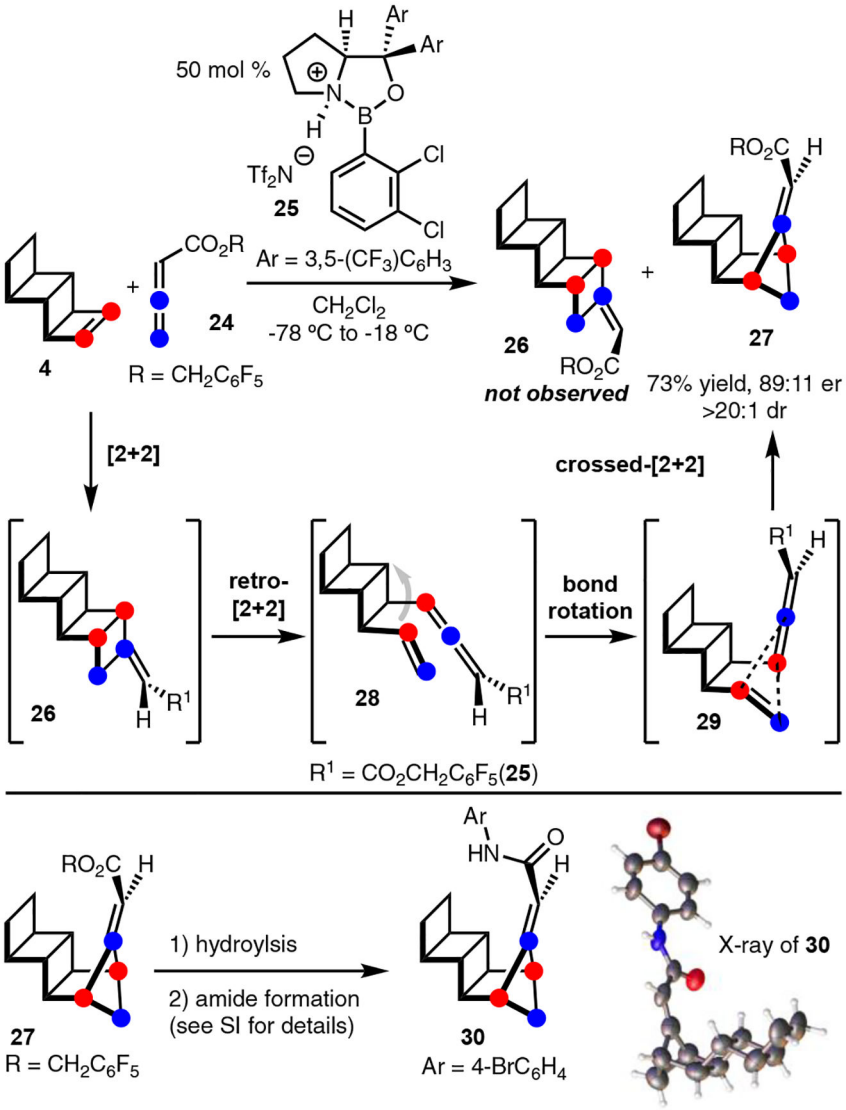
Scheme 3.

Attempted Synthesis of [4]-Ladderene **4**.

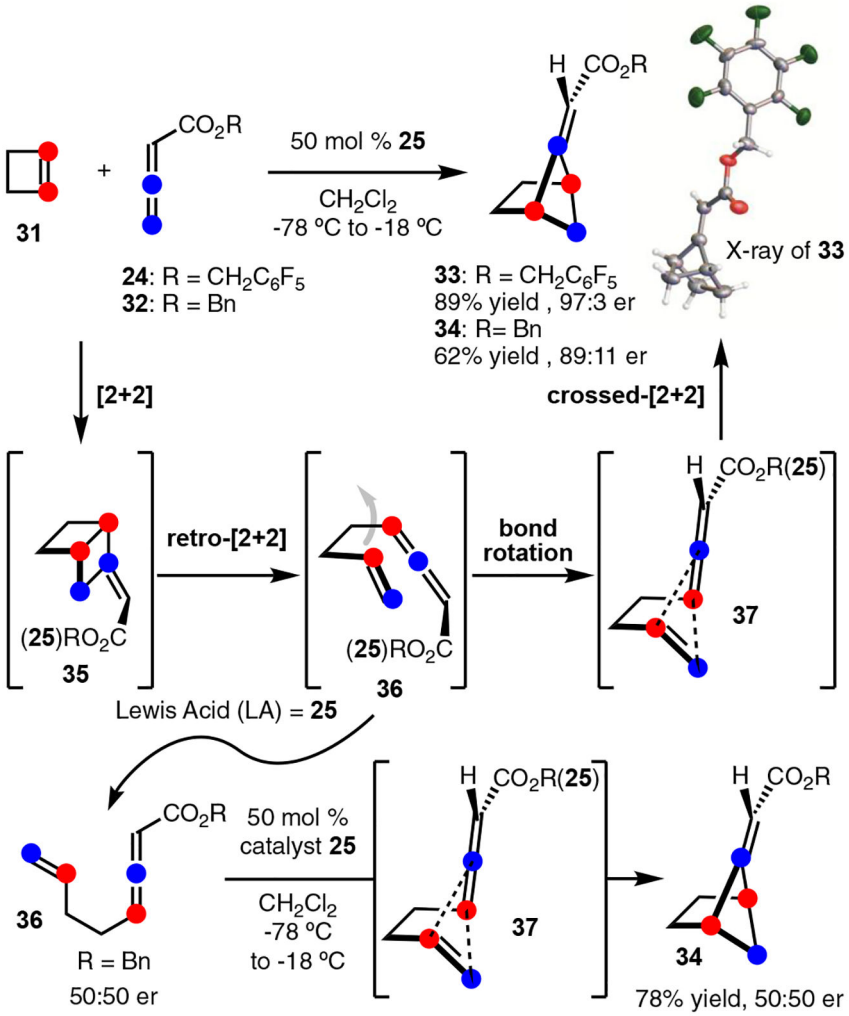


Scheme 4.

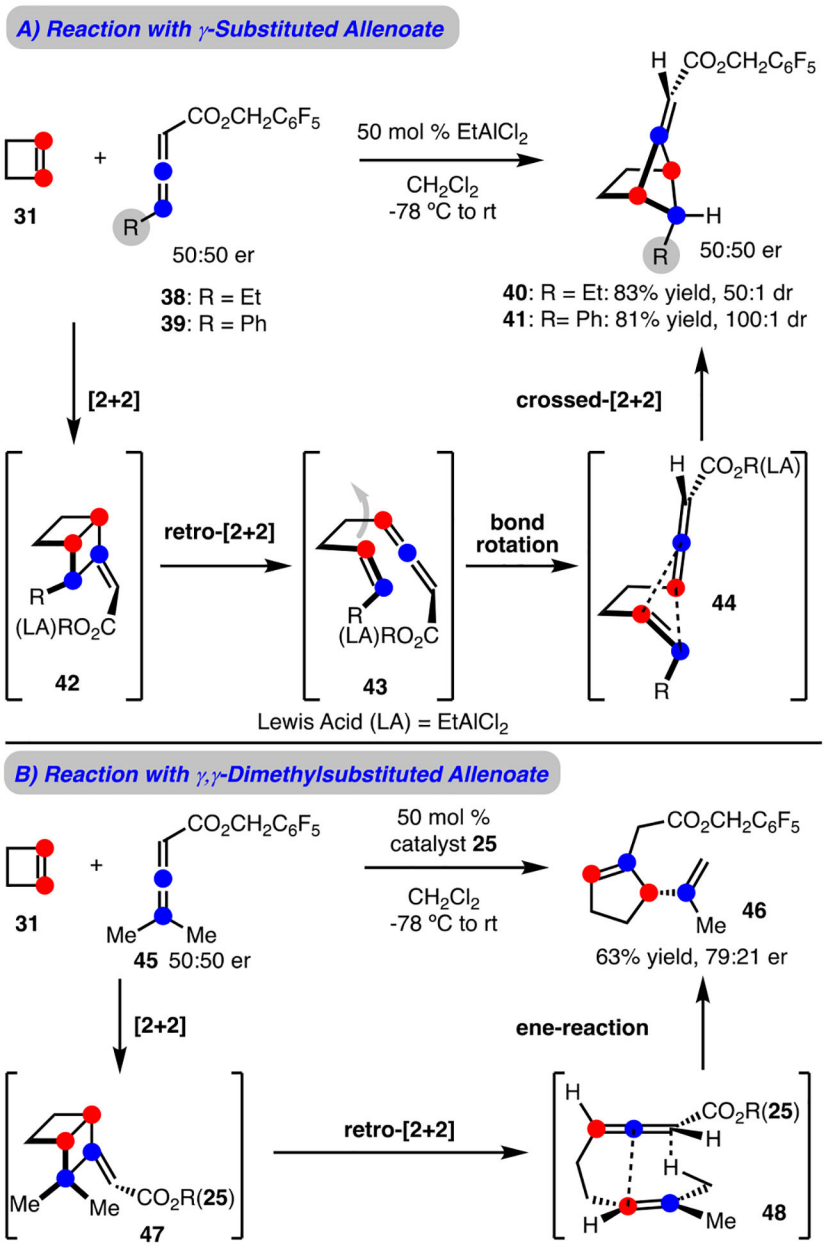
Synthesis of [4]-Ladderene **4**. T3P = 1-Propanephosphonic anhydride. *p*-ABSA = 4-Acetamidobenzenesulfonyl azide.



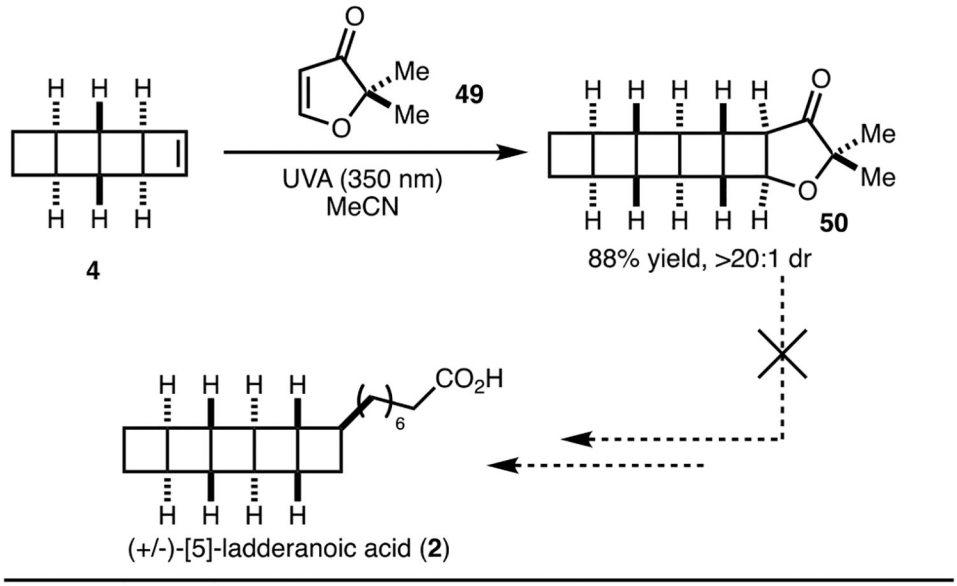
Scheme 5.
Ring Strain Induced Pericyclic Cascade.



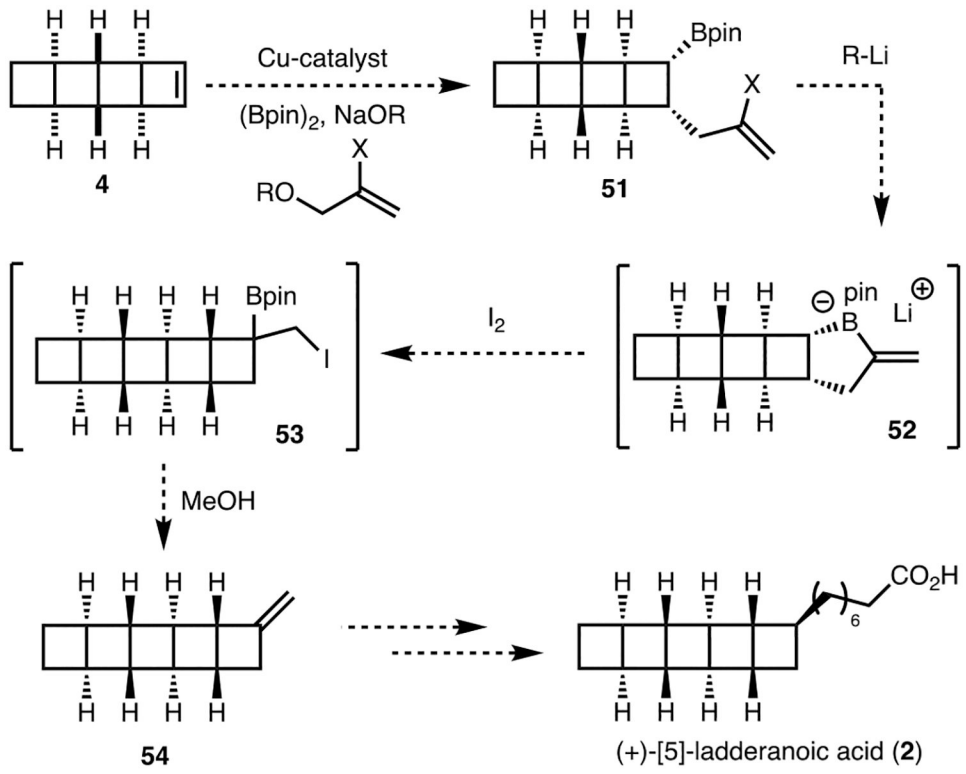
Scheme 6.
Mechanism Studies.



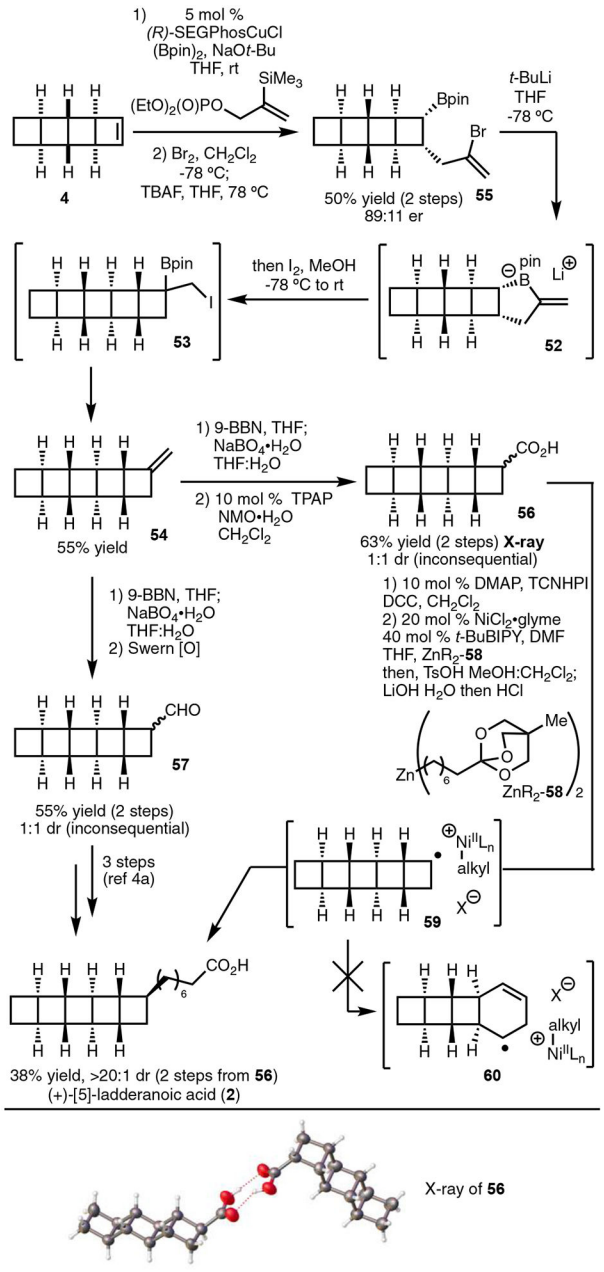
Scheme 7.
Reactions with Substituted Allenoates.



Scheme 8.
Cycloaddition with Furenone **49**.



Scheme 9.
Second Generation Strategy.



Scheme 10.

Completion of the Synthesis of (+)-[5]-Ladderanoic Acid. TCNHPI = Tetrachloro-*N*-hydroxyphthalimide.