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

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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 occurrence required a drastic revision of the synthetic design that ultimately led to the development of a novel stepwise cyclobutane assembly by an allylboration/Zweifel olefination sequence.

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 either 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. Because of their complex structure and unknown biological function, several groups have developed routes to these molecules (Scheme 1). In 2006, Corey et al. reported a synthesis of (+)-[5]-ladderanoic acid ([+]-2), and it featured a diastereoselective photochemical [2+2] cycloaddition. Ten years later, Burns et al. reported elegant syntheses of (-)[5]-ladderanoic acid ([−]-2), (+)-[3]-ladderanol ([+]-1), and the fully assembled phospholipid 3. The approach towards (-)-2 featured a Mn-catalyzed C–H chlorination and a desymmetrization by an enantioselective Cu-catalyzed protoboration. In the case of 1, a diastereoselective [2+2] cycloaddition established the core structure.

Given our group’s long-standing interest in the chemistry surrounding cyclobutanes, we recently reported a synthesis of (-)-[3]-ladderanol ([−]-1). 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 (+)-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 (+)-2 hinged on a late-stage enantioselective [2+2] cycloaddition between the [4]-ladderene 4 and an allenate to assemble the final cyclobutane (Scheme 2A). Conversion of the cycloadduct into the target was envisioned to occur through a chain elongation sequence. Inspiration for the proposed [2+2]
cycloaddition stemmed from early work in our group on related cycloadditions.\(^7\) In these reactions, a wide variety of alkenes, such as cyclopentene (5), could be converted into the products through a \([2+2]\) cycloaddition promoted by oxababorolidine catalysts (e.g., 8) with good levels of enantioselectivity (Scheme 2B).

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

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

An alternative strategy was developed to access 4 through implementation of a \([2+2]\) cycloaddition with cyclopentenone and subsequent ring contraction by Wolff rearrangement (Scheme 4). Design of this strategy was influenced by the proclivity of photochemical \([2+2]\) cycloadditions to use cyclopentenone (17)\(^{10}\) and prior studies from the Corey group and our group in the synthesis of related structures.\(^{4,6}\)

As such, the synthesis commenced with cycloaddition between 17 and 1,2-dichloroethylene to generate the [3.2.0]-bicycloheptane 18. Ketone formation and reduction of the dichloride resulted in the cyclobutene 19. A second photochemical \([2+2]\) cycloaddition with 17 gave rise to 20 as an inconsequential mixture of regioisomers. Diazo formation and subsequent Wolff rearrangement ultimately provided the carboxylic acid 21. Decarboxylation followed by a similar series of transformations provided access to the [4]-ladderane carboxylic acid 23. Conversion of the carboxylic acid into the bromide followed by elimination led to 4.

With synthesis of 4 completed, the key enantioselective cycloaddition with the allenolate 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 the oxazaborolidene 25 was used. However, upon rigorous structural determination by X-ray crystallography of a derivative (30), it was revealed that the [2.1.1]-bicycle 27 was formed as the exclusive product. This remarkable transformation is proposed to occur by initial [2+2] cycloaddition to generate the desired cycloadduct 26 as outlined in Scheme 5. However, because of the inherent ring strain, a retro-[2+2] cycloaddition occurs rapidly to generate the 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 (oB97X-D/6-311 + G(d,p); see the Supporting Information for details) revealed that 27 is 8 kcal mol⁻¹ lower in energy than 26. While the process shown in Scheme 5 has not been reported to the best of our knowledge, a related ketene–allenoate [2+2]-retro-[2+2] cycloaddition has been disclosed. [7]

Two additional points regarding this reaction are important to note: 1) When the reaction is monitored by ¹H NMR spectroscopy (500 MHz), no intermediates that would correspond to either 26 or 28 are detected. This data suggests that the initial [2+2] is rate determining, with rapid subsequent steps. 2) The process is not limited to 4, as reaction of cyclobutene (31) was also found to generate the analogous [2.1.1]-bicyclic products 33 and 34 (Scheme 6). This reaction likely proceeds via chiral allenoate 24. It is interesting that 33 (and likely 34 by analogy) were found to be 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 in the initial [2+2] cycloaddition of [4]-ladderene and cyclobutene. While the basis of this remains unclear, alkene–allenoate [2+2] cycloadditions have been reported with varying degrees of E/Z selectivities.[7]

To further probe the proposed mechanism, 36 was independently prepared (Scheme 6). Subjection of 36 to the reaction conditions generated the [2.1.1]-bicyclic product 34. This observation supports the hypothesis that 36 could be an intermediate in the conversion of cyclobutene and allenoates 24 and 32 into products 33 and 34, respectively. This product is formed in 50:50 e.r. because the prepared allenoate is also racemic.

Given the unusual nature of the pericyclic cascade, several other allenoates were evaluated in the transformation (Scheme 7). Reaction with the γ-substituted allenoates 38 and 39 led to the expected [2.1.1] bicyclic products 40 and 41, respectively, with high levels of diastereoselectivities. The reaction likely proceeds in an analogous manner to that of the unsubstituted allenoate. To rationalize the formation of the observed diastereomer, [2+2] cycloaddition must occur to generate the diastereomer 42 in which the R group is located on the concave face of the [2.2.0]-bicycle. Finally, while EtAlCl₂ was found to be the optimal promoter, the catalyst 25 was also competent yet give rise to several unidentified byproducts.[15]

Reaction with the γ,γ-dimethylsubstituted allenoate 45 and cyclobutene did not give rise to the expected [2.1.1]-
bicyclic product but rather the 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 because of steric considerations of a four-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 e.r. (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 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 requirement 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 could undergo photoaddition with 49 to install the final cyclobutane ring (product 50). However, elaboration of this compound into the target proved challenging, mainly because of 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. Given our group’s interest in arylborination reactions of alkenes,18 we devised a second-generation strategy that would involve allylboration (4→51) followed by Zweifel olefination (51→54; Scheme 9). Inspiring studies from the groups of Hoveyda19 and Yun20 on Cu-catalyzed enantioselective allylboration of styrenyl derivatives and borylcupration of cyclobutenes from the groups of Tortosa21 and Burns22 suggested that 51 could be prepared by merging the two methods (Scheme 9). While Zweifel olefination is well established in intermolecular variants,22,23 intramolecular reactions are rare. In only one example, Aggarwal and co-workers 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 was implemented to generate (+)-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 through treatment with \( \text{Br}_2 \) followed by TBAF. Addition of \( \text{iBuLi} \) to the vinyl bromide resulted in generation of borate \( \text{S}2 \) which underwent reaction smoothly with \( \text{I}_2 \) to generate \( \text{S}4 \) after 1,2-elimination (via \( \text{S}3 \)).

The [5]-methylene ladderane \( \text{S4} \) could be elaborated to (+)-2 through one of two routes (Scheme 10). The first involved a hydroboration-oxidation with 9-BBN followed by Swern oxidation to the aldehyde \( \text{S7} \). Intermediate \( \text{S7} \) can be converted into (+)-2 through an epimerization, Wittig olefination, and diimide reduction sequence as demonstrated by Corey et al.\(^{[44]}\). Alternatively, we elected to explore an approach that would take advantage of an emerging set of reactions introduced by Baran and co-workers, specifically decarboxylative alkyl-alkyl cross-coupling.\(^{[25]}\) In this approach, \( \text{S4} \) was converted into the carboxylic acid \( \text{S6} \) through a hydroboration-oxidation sequence. Synthesis of the redox active ester, subsequent Ni-catalyzed cross-coupling with the dialkylzinc reagent \( \text{S8} \), and hydrolysis provided (+)-2 in 38\% yield over two steps.\(^{[26]}\) It is interesting to note that the Ni-stabilized cyclobutyl radical \( \text{S9} \), or related alkylsilane free radicals generated in the decarboxylative transformation \( \text{S11} \) into \( \text{S12} \) and \( \text{S13} \) into \( \text{S4} \) do not undergo strain release promoted ring-opening.\(^{[27]}\) DFT calculations (\( \text{B97X-D/6-311G(d,p)} \)); see the Supporting Information for details) reveal that the free radical of \( \text{S6} \) (no Ni) is 27 kcal mol\(^{-1} \) lower in energy than the free radical of \( \text{S9} \) (no Ni). In addition, the predicted barrier for conversion of the free radical of \( \text{S9} \) into \( \text{S6} \) is only 18 kcal mol\(^{-1} \). This data suggests that bimolecular capture of the cyclobutyl free radicals is rapid.

**Conclusion**

In summary, an evolution of a strategy to prepare (+)-[5]-ladderanoic acid [(+)-2] 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.

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Conflict of interest

The authors declare no conflict of interest.

Stichwörter: Cycloadditionen · Geeignete Moleküle · Kupfer · Naturstoffe · Reaktionsmechanismen

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[9] The discrepancy in quantities of ethylene and methylbenzoate is likely due to ethylene in the headspace of the flask.


[14] Use of other Lewis acids or esters was attempted. When conversion was observed only the [2,1.1]-bicycle was observed. See the Supporting Information for details.

[15] The products 40 and 41 were formed in low enantioselectivity accompanied by other isomers with promoter 25.


[17] See the Supporting Information for details.


[26] The natural product generated in this way is contaminated with octanoic acid (derived from hydrolysis of 58), which could not be separated because of similar physiochemical properties.


[28] CCDC 910901, 1963457, and 1963458 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.