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Synthesis of *ent*-[3]-Ladderanol: Development and Application of Intramolecular Chirality Transfer [2+2] Cycloadditions of Allenic Ketones and Alkenes

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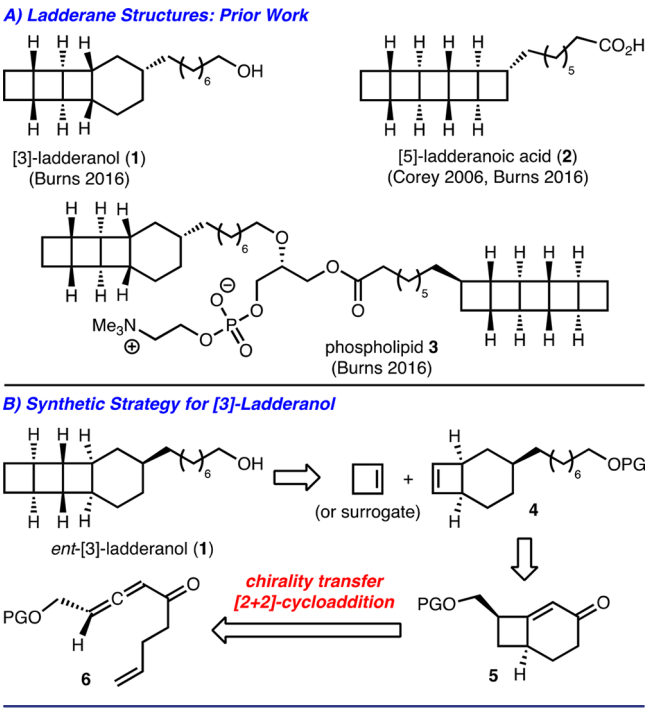
Supporting Information

ABSTRACT: An enantioselective synthesis of *ent*-[3]-ladderanol is presented. The ladderanes are an interesting class of molecules for their unique structure of fused cyclobutane rings as well as their perceived biological function of organism protection. The route hinges on the development and application of a chirality transfer [2+2] cycloaddition of an allenic ketone and alkene. Further stereocontrolled transformations allowed for completion of the synthesis. The scope of the chirality transfer [2+2] cycloaddition is also presented.

The ladderane family of natural products (Scheme 1A), isolated in 2002 from the annamox bacteria, is an intriguing class of molecules due to their highly unusual structure of fused cyclobutane rings and their perceived biological function of organism protection.[1] It has been postulated that the ladderane incorporates into the lipid bilayer to render a denser cell membrane, which contributes to a tighter barrier against diffusion of toxic intermediates.[2,3] This process is crucial to the survival of the organism as it compartmentalizes toxic N_2H_4, which is an intermediate in the conversion of NH_4^+ and NO_2^- to N_2 and $2H_2O$ for energy production. Due to the paucity of these molecules from biological sources, unconfirmed function, and interesting structure, which could inspire new strategies/methods, we sought to develop a synthesis of these molecules.[4] At the outset of our studies, only one enantioselective synthesis of [5]-ladderanoic acid (**2**) was known and was reported by Corey in 2006.[5] Therefore, we initially targeted the synthesis of [3]-ladderanol (**1**). However, during our efforts, Burns and co-workers developed a synthesis of [3]-ladderanol (**1**), [5]-ladderanoic acid (**2**), as well as the fully assembled phospholipid (**3**).[6]

Our synthetic design is illustrated in Scheme 1B. We envisioned that the three fused cyclobutanes could be assembled by a late-stage [2+2] cycloaddition between cyclobutene **4** and cyclobutene itself (or a surrogate). Further disconnection of **4** by stereocontrolled transformations revealed [4.2.0]-bicycle **5**. Inspired by our group's previous efforts toward development of allenoate alkene [2+2] cycloadditions,[7,8] a strategy was devised in which **5** could be prepared by intramolecular cycloaddition of allenic ketone **6**.[9,10] This cycloaddition is notable in that it would represent an unusual chirality transfer [2+2] cycloaddition.[11]

Scheme 1. Prior Work and Synthetic Strategy



To implement the strategy outlined in Scheme 1B, a straightforward and enantioselective synthesis of allenic ketone **6** was required. Although enantioselective synthesis of allenic ketones is unprecedented, we were encouraged by known methods for the enantioselective synthesis of allenoates by enantioselective isomerization of β,γ-alkynyl esters.[12,11f] Application of this methodology required the synthesis of β,γ-alkynyl ketone **9**, which was accomplished by a two step protocol involving addition of the acetylide derived from **7** to epoxide **8** and subsequent oxidation with Dess-Martin periodinane (Scheme 2). With access to β,γ-alkynyl ketone **9**, it was determined that the enantioselective isomerization could be promoted by thiourea catalyst **10** to provide the allene **11**.[13−15] Direct addition of $MeNO_2$ and $Bi(OTf)_3$ to the reaction mixture allowed for chirality transfer [2+2] cycloaddition to generate **13** in 57% yield and 94:6 er.[9,16] It should be noted that while the allene was not isolated in the

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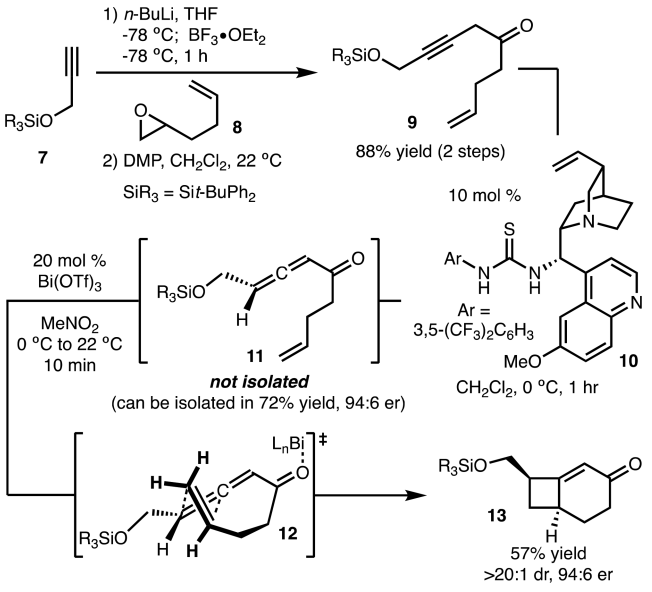
Scheme 2. Chirality Transfer [2+2] Cycloaddition



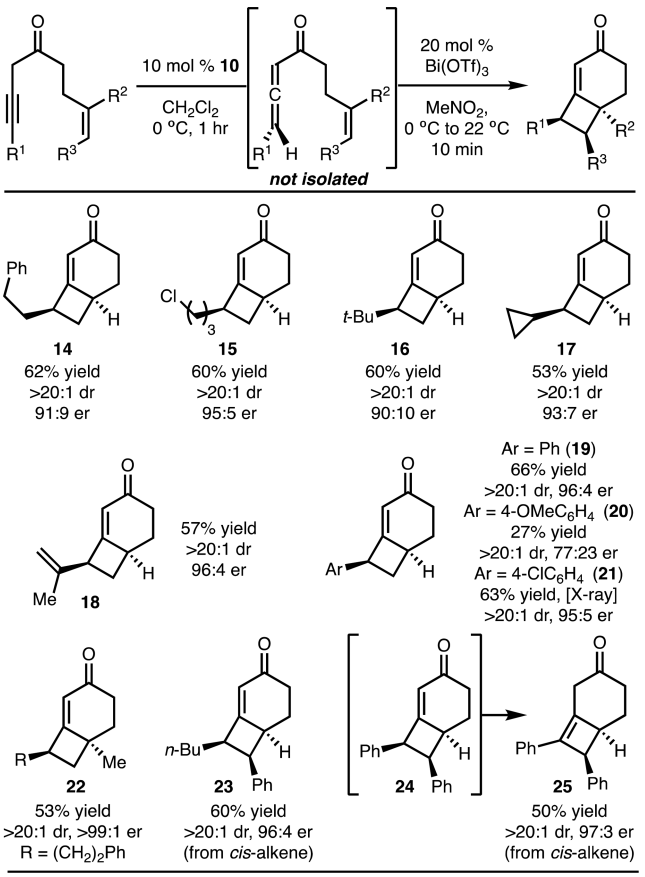
synthesis of **13**, it could be isolated in 72% yield and 94:6 er. A model for the chirality transfer [2+2] cycloaddition is illustrated in Scheme 2 (**12**). The alkene tether likely approaches the allene distal to the larger $-CH_2OSiR_3$ group. In addition, the alkene is aligned perpendicular to the allene in accordance with models proposed for related ketene-alkene [2+2] cycloadditions.[17]

We have found this sequence to be a generally effective method for the enantioselective synthesis of [4.2.0]-fused bicycles (Scheme 3). The γ-substituent of the allene could be varied from *n*-alkyl (products **14** and **15**) to sterically demanding cyclopropyl or *t*-butyl groups (products **16** and **17**, respectively). Vinyl and aryl groups were also tolerated (products **18**, **19**, **21**, respectively); however, one notable exception is that reaction with an electron-rich aryl group led to formation of **20** in low yield and enantioselectivity. In this example, the rate of cycloaddition was reduced, which likely allowed for competitive racemization of the allene prior to cycloaddition.

With regard to the alkene tether, this method permits access to the formation of product **22**, which contains a quaternary center, in good yield and enantioselectivity (Scheme 3). Reaction with a *cis*-1,2-disubstiuted alkene resulted in formation of product **23** as a single diastereomer. The preservation of the alkene geometry in product **23** suggests a cycloaddition that is stereospecific in nature. Therefore, it is proposed that the cycloaddition proceeds through a concerted mechanism, or at least involves a short-lived intermediate.[17,18] Reaction with a related substrate led initially to the formation of **24**; however, upon purification cycloadduct **25** was isolated. This is likely due to two factors: (1) destabilization of **24** from the eclipsing Ph groups, and (2) stabilization of **25** by formation of a conjugated alkenylarene.

Having established an efficient method for the synthesis of **13**, advancement to **27** was readily accomplished through a four-step sequence (Scheme 4). Stereoselective 1,4-reduction of **13** with L-selectride and enol triflate formation allowed for the corresponding trisubstituted alkene. Negishi cross-coupling with zinc reagent **26** promoted by Pd-CPhos-

Scheme 3. Chirality Transfer [2+2] Cycloaddition: Scope[a]



[a]See the Supporting Information for details. Yield of isolated product after purification. Average of two experiments (0.5 mmol). Enantiomeric ratio (er) determined by HPLC analysis with a chiral column.

G3[19,20] and stereoselective hydrogenation from the convex face with Crabtree's catalyst[21] furnished **27**, after deprotection with TBAF, as a single diastereomer in 69% yield over four steps. Oxidation to the carboxylic acid followed by decarboxylation in the presence of $BrCCl_3$ allowed for formation of the corresponding cyclobutyl bromide in 7:3 dr.[22] Treatment of this mixture with $KOSiMe_3$ provided **28** as well as unreacted minor diastereomer of bromide, which was separable by chromatography.[23]

Several strategies were envisioned for the completion of the synthesis (Scheme 4). Initially, a direct [2+2] cycloaddition of cyclobutene and **28** was attempted on the basis of seminal reports from Hill and Koichi.[24] Under various conditions, however, <2% of the cycloadduct was observed, which is likely due to the difficulties associated with photoexcitation (with or without a sensitizer) of cyclobutene without photoinduced decomposition of the starting material. Efforts were directed toward the exploration of a photocycloaddition with cyclobutene ester/acid (**29**) based off reports from Wender.[25] In this case, while trace quantities of the cycloadduct were observed, optimization did not lead to notable improvements.

Since the [2+2] cycloaddition with cyclobutene or **29** proved to be challenging, we directed our efforts toward cyclopentenone as this is well-known to undergo reaction with a variety of alkenes.[26] This strategy would require a ring contraction, which we reasoned could be accomplished by

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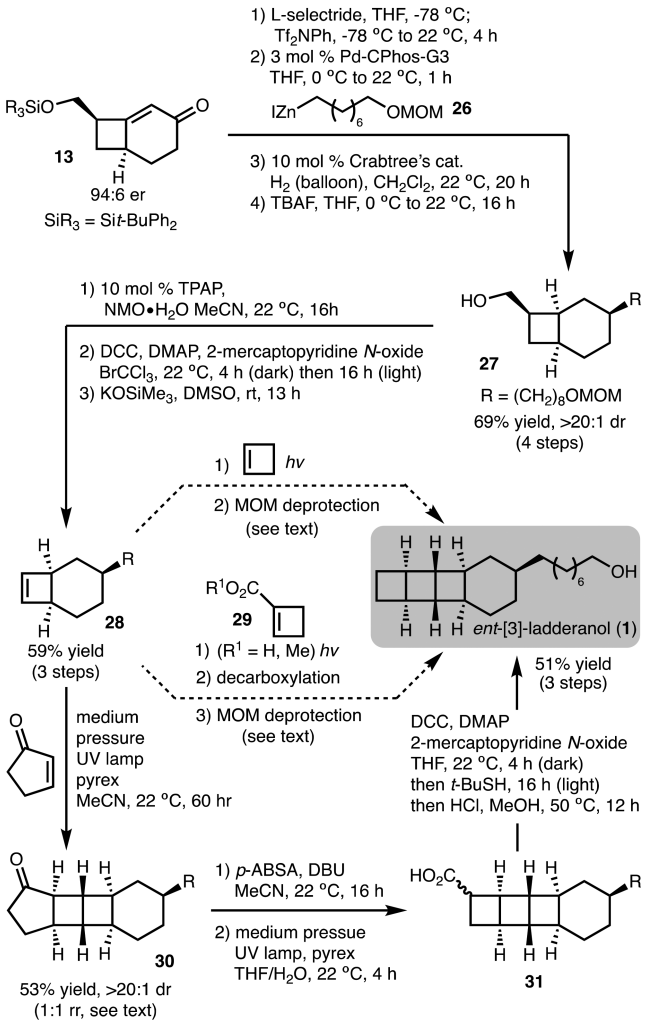
application of the Favorskii[27] or Wolff rearrangements.[5b,28] In the event, stereoselective cycloaddition of cyclobutene **28** with cyclopentenone led to formation of **30** as a mixture of regioisomers (only one shown as it is inconsequential to the synthesis) (Scheme 4). While attempted application of the

Scheme 4. Synthesis of *ent*-[3]-Ladderanol (1)



Favorskii rearrangement was unsuccessful, it was identified that Wolff rearrangement of the generated α-diazoketone allowed for synthesis of **31** as an inconsequential mixture of diastereomers. Completion of the synthesis of *ent*-[3]-ladderanol was accomplished by decarboxylation and subsequent deprotection of the MOM group upon workup in 51% yield over three steps. The final step of the sequence was carried out starting with 160 mg of **31** to provide 95 mg of *ent*-[3]-ladderanol (**1**).

In summary, a synthesis of *ent*-[3]-ladderanol has been accomplished in 14 steps from readily available components **7** and **8**. This synthesis serves to showcase that targeting structurally interesting compounds can serve as a source of inspiration for the development of new methods. As such, these efforts have led to the development of a chirality transfer [2+2] cycloaddition of allenic ketones and alkenes to provide rapid access to [4.2.0]-bicycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b09844.

Experimental procedures (PDF)
Analytical data (IR, ^{1}H and ^{13}C NMR and HRMS) for all new compounds (PDF)
X-ray crystallographic data for **21** (CIF)

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Author Contributions

#These authors contributed equally to the completion of this work.

Notes

The authors declare no competing financial interest.

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