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A modular approach to prepare enantioenriched cyclobutanes: synthesis of (+)-rumphellaone A†

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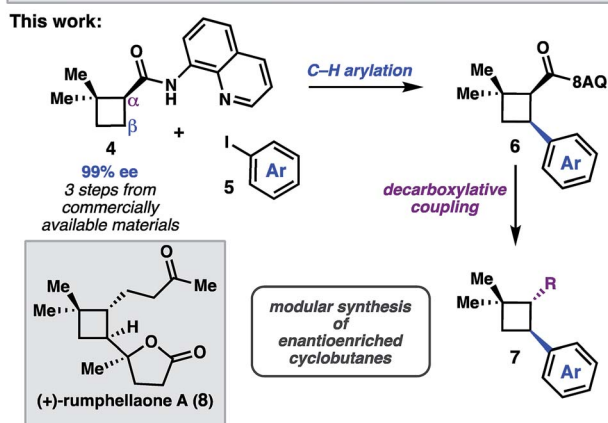
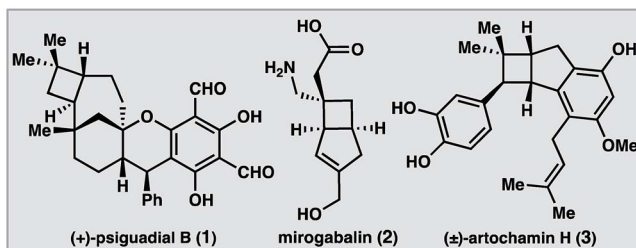
A modular synthesis of enantioenriched polyfunctionalized cyclobutanes was developed that features an 8-aminoquinolinamide directed C–H arylation reaction. The C–H arylation products were derivatized through subsequent decarboxylative coupling processes. This synthetic strategy enabled a 9-step enantioselective total synthesis of the antiproliferative meroterpenoid (+)-rumphellaone A.

Introduction

The cyclobutane structural motif is present in a variety of natural products and pharmaceutical molecules (Scheme 1).^{1,2}

Cyclobutanes are also versatile synthetic intermediates, as the ring strain inherent to these structures engenders them with unique reactivity that can be leveraged in a variety of transformations to build complex frameworks.³ [2 + 2] cycloaddition reactions represent the most extensively developed approach to construct cyclobutanes, and recent advances have given rise to elegant enantioselective reactions.⁴ An alternative strategy is to prepare a versatile cyclobutane building block, and then use C–H functionalization or cross-coupling chemistry to elaborate the scaffold in a modular fashion.⁵ In this latter approach, a single enantioenriched intermediate can quickly be converted to a variety of more functionalized structures.

We recently reported a synthesis of the natural product (+)-psiguadial B (1), which featured a tandem Wolff-rearrangement/asymmetric ketene addition to prepare enantioenriched 8-aminoquinolinamide 4 (Scheme 1).⁶ Given the short synthesis of 4 from commercial starting materials, we became interested in further applications of this chiral building block. Specifically, we envisioned that directed C–H arylation could enable diversification at the β-position,⁷ while hydrolysis of the 8-aminoquinolinamide followed by decarboxylative radical cross-coupling could enable diversification at the α-position. A number of powerful methods have been developed that leverage the decarboxylative formation of carbon-centered radicals for C–C and C–X bond formation.⁸ It was anticipated that the sequence of C–H arylation followed by decarboxylative coupling could provide access to a collection of enantioenriched polyfunctionalized cyclobutanes.



Scheme 1 A C–H functionalization strategy to access (+)-rumphellaone A.

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Results and discussion

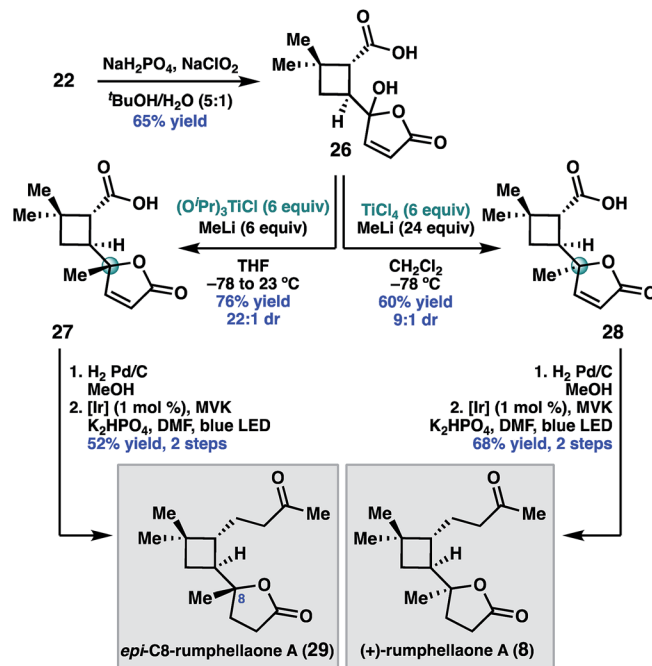
We began by investigating the scope of the directed C–H arylation of 8-aminoquinolinamide 4, which was prepared in three steps and 99% ee from commercially available 2,2-dimethylcyclopentan-1-one.⁶ Using our previously developed conditions [Pd(OAc)₂ (15 mol%), Ag₂CO₃ (1.0 equiv.), aryl iodide (2.0 equiv.), TBME, 90 °C], a series of *cis*-arylated cyclobutanes were



through the C1–C2 bond to give **21** (Scheme 4); in the forward sense, the ketone fragment would be incorporated through a decarboxylative Giese addition with methyl vinyl ketone. The butenolide of **21** could derive from oxidation of furan **22**, which could be prepared from **4** by a directed C–H arylation. As a proof of concept, 8-aminoquinolinamide **4** was subjected to Pd-catalyzed C–H functionalization with furanyl iodide **23** to give *cis*-cyclobutane **24** in 90% yield.¹⁵ Hydrolysis and subsequent decarboxylative Giese reaction with methyl vinyl ketone under photoredox catalysis provided **25** in 50% yield over two steps.¹⁶

Having validated the feasibility of the two key cyclobutane functionalization reactions, attention turned to the unmasking of the butenolide functionality prior to the decarboxylative Giese reaction. Treatment of **22** with sodium chlorite under buffered conditions¹⁷ delivered 5-hydroxybutenolide **26** (Scheme 5). The remaining challenge was installation of the C8 methyl substituent with the required *S*-configuration. In prior syntheses of **8**, this stereogenic center was set under the guidance of chiral catalyst control.¹⁴ Given that the C8 diastereomers were inseparable by column chromatography, high diastereoselectivity for this methyl addition was important.

After exploring a range of conditions to effect the methylation, we were pleased to discover that either C8 diastereomer (**27** or **28**) could be prepared using the appropriate methyltitanium reagent. Thus, addition of **26** to a pre-formed 1 : 1 mixture of $(^i\text{PrO})_3\text{TiCl}$ and MeLi at -78°C , with warming to 23°C , delivered the undesired C8 diastereomer, **27**, in 76% yield and 22 : 1 dr.¹⁸ Alternatively, addition of **26** to a -78°C solution of $\text{Ti}(\text{Me})_4$ in dichloromethane,¹⁹ which was prepared *in situ* by combining MeLi and TiCl_4 in a 4 : 1 ratio, provided the desired diastereomer **28** in 60% yield and 9 : 1 dr. We hypothesize that the divergent diastereoselectivity for these two reactions resulted from the different methylating reagents, $(^i\text{PrO})_3\text{TiMe}$ or $\text{Ti}(\text{Me})_4$,



Scheme 5 Synthesis of (+)-rumphellaone A (**8**).

prepared *in situ*. One possible explanation is that **27** formed by ligand exchange of the carboxylic acid of **26** with $(^i\text{PrO})_3\text{TiMe}$ followed by intramolecular delivery of the methyl nucleophile, while **28** resulted from addition of $\text{Ti}(\text{Me})_4$ without the assistance of chelation.

To complete the synthesis, **28** was reduced under standard hydrogenation conditions. Decarboxylative Giese addition of **28** to methyl vinyl ketone under photoredox catalysis provided (+)-rumphellaone A (**8**) in good yield, completing the synthesis in 9 steps from commercially available material. Epimeric acid **27** could be analogously elaborated to (+)-*epi*-C8-rumphellaone A (**29**).

Conclusions

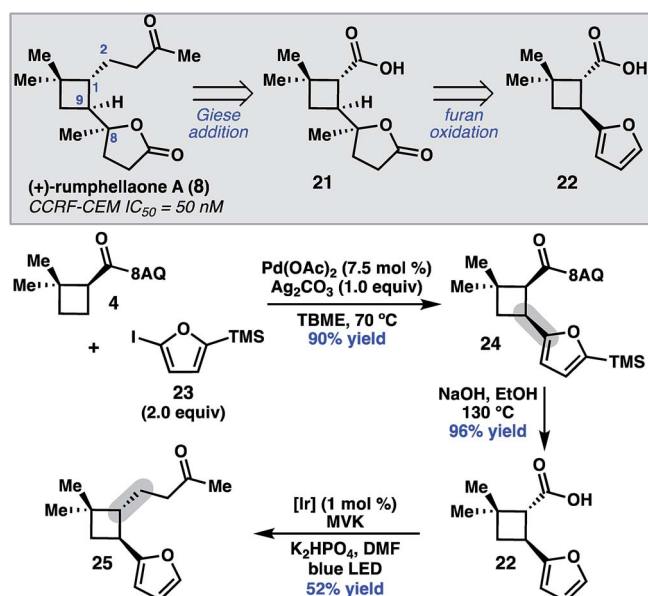
Through a strategy for difunctionalization, we have demonstrated that 8-aminoquinolinamide **4** can serve as a valuable building block for the synthesis of enantioenriched cyclobutanes. We further illustrated this concept in a 9-step synthesis of (+)-rumphellaone A (**8**). We anticipate that this general strategy could enable the expedient synthesis of additional natural products and other bioactive molecules.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Scheme 4 Retrosynthetic analysis of **8** and key proof-of-concept study. TMS = trimethylsilyl. MVK = methyl vinylketone.



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