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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

prepared in good yields (Scheme 2).⁹ The reaction was compatible with both electron-rich and electron-deficient aryl iodides and tolerated substitution at the *ortho*, *meta*, and *para* positions. Heteroaryl iodides were also found to be competent coupling partners, allowing for incorporation of pyridines, pyrimidines, and indoles. Unfortunately, with 5-iodo-2-phenylpyridine or 5-iodo-2-methoxypyrimidine, the reaction proceeded in only modest yields (<40%). Aryl triflates failed to react under the optimized reaction conditions.

Having established the generality of the C–H arylation step, we turned our attention to diversification at the carbon bearing the 8-aminoquinolinamide through functional group interconversion or decarboxylative cross-coupling. To this end, hydrolysis of **9d** proceeded with epimerization to the thermodynamically favored *trans* diastereomer, delivering *trans*-cyclobutanoic acid **10** (Scheme 3).¹⁰ Reduction of the acid delivered alcohol **12**, which could be oxidized under Stahl conditions to aldehyde **13**.¹¹ Alternatively, **10** could be converted to the corresponding acid chloride and engaged in a nickel-catalyzed reductive cross-coupling with iodocyclohexane to access ketone **14**.¹² In order to investigate decarboxylative coupling processes, acid **10** was subjected to EDC-mediated coupling with *N*-hydroxyphthalimide to provide NHP ester **11**.¹³ Ni-catalyzed coupling of **11** with arylzinc chloride **15** gave



Scheme 2 Scope of the C–H arylation of **4**. Reactions were conducted on 0.20 mmol scale in a sealed 2-dram vial using Pd(OAc)₂ (15 mol %), Ag₂CO₂ (1.0 equiv.), **5a–p** (2.0 equiv.), [**4**] = 0.2 M in TBME. TBME = *tert*-butyl methyl ether.



Scheme 3 Selected derivatizations of **10**. ABNO = 9-azabicyclo[3.3.1]nonane *N*-oxyl. NMI = *N*-methylimidazole. NHPI = *N*-hydroxyphthalimide. EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. DMAP = 4-dimethylaminopyridine. TFA = trifluoroacetic acid. dtbbpy = di-*tert*-butylbipyridine. dme = dimethoxyethane. 4,4'-MeObpy = 4,4'-dimethoxybipyridine. [Ir] = Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆.

trans-diarylcyclobutane **16** in good yield as a single diastereomer.^{8d} Similarly, NHP ester **11** underwent Ni-catalyzed reductive alkenylation with styrenyl bromide **17** to furnish cyclobutane **18** in 56% yield.^{8c,e} Photoinduced decarboxylative borylation of **11** proceeded smoothly to afford boronic ester **19**.⁸ⁱ

To further demonstrate the utility of this cyclobutane difunctionalization strategy, we designed and executed a synthesis of the natural product (+)-rumphellaone A (**8**).¹⁴ (+)-Rumphellaone A (**8**) was isolated in 2010 from the gorgonian coral *Rumphella antipathies* and possesses anti-proliferative activity against human T-cell acute lymphoblastic leukemia tumor cells.^{2d} Retrosynthetically, we envisioned disconnecting

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*PrO)₃TiCl 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 Ti(Me)₄ in dichloromethane,¹⁹ which was prepared *in situ* by combining MeLi and TiCl₄ 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*PrO)₃TiMe or Ti(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*PrO)₃TiMe followed by intramolecular delivery of the methyl nucleophile, while **28** resulted from addition of Ti(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.

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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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