

Cite this: *Chem. Sci.*, 2019, 10, 2315

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 6th December 2018
Accepted 19th December 2018

DOI: 10.1039/c8sc05444d

rsc.li/chemical-science

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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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8sc05444d

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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 **20**,^{8h} and decarboxylative Minisci type arylation of **11** under photoredox catalysis delivered quinoline **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.

Acknowledgements

We thank Dr Scott Virgil and the Caltech Center for Catalysis and Chemical Synthesis for access to analytical equipment. Fellowship support was provided by an NIH Training Grant (J.



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



C. B., Grant No. 5T32GM007616-39) and the NSF (C. R. L. and L. M. C., Grant No. DGE-1144469) and S. E. R. is a Heritage Medical Research Foundation Investigator. Partial financial support from the NSF (CAREER-1057143) and NIH (R35GM118191-01), as well as the Research Corporation Cottrell Scholars program, is gratefully acknowledged.

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