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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 **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.

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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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Notes and references

- (a) V. M. Dembitsky, *J. Nat. Med.*, 2008, **62**, 1–33; (b) Y. J. Hong and D. J. Tantillo, *Chem. Soc. Rev.*, 2014, **43**, 5042–5050; (c) R. M. Ortuno, A. G. Moglioni and G. Y. Motrasio, *Curr. Org. Chem.*, 2005, **9**, 237–259.
- (a) Psigudial B: M. Shao, Y. Wang, Z. Liu, D.-M. Zhang, H.-H. Cao, R.-W. Jiang, C.-L. Fan, X.-Q. Zhang, H.-R. Chen, X.-S. Yao, *et al.*, *Org. Lett.*, 2010, **12**, 5040–5043; (b) Mirogabalin: A. Vinik, J. Rosenstock, U. Sharma, K. Feins, C. Hsu and D. Merante, *Diabetes Care*, 2014, **37**, 3253–3261; (c) Artochamin H: Y.-H. Wang, A.-J. Hou, D.-F. Chen, M. Weiller, A. Wendel and R. J. Staples, *Eur. J. Inorg. Chem.*, 2006, **15**, 3457–3463; (d) Rumphellaone A: H.-M. Chung, Y.-H. Chen, M.-R. Lin, J.-H. Su, W.-H. Wang and P.-J. Sung, *Tetrahedron Lett.*, 2010, **51**, 6025–6027.
- (a) T. Seiser, T. Saget, D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2011, **50**, 7740–7752; (b) J. C. Namyslo and D. E. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485–1538; (c) E. Lee-Ruff and G. Mladenova, *Chem. Rev.*, 2003, **103**, 1449–1484; (d) M. Wang and P. Lu, *Org. Chem. Front.*, 2018, **5**, 254–259.
- (a) R. Brimioulle and T. Bach, *Science*, 2013, **342**, 840–843; (b) J. Du, K. L. Skubi, D. M. Schultz and T. P. Yoon, *Science*, 2014, **344**, 392–396; (c) N. Vallavoju, S. Selvakumar, S. Jockusch, M. P. Sibi and J. Sivaguru, *Angew. Chem., Int. Ed.*, 2014, **53**, 5604–5608; (d) M. L. Conner, Y. Xu and M. K. Brown, *J. Am. Chem. Soc.*, 2015, **137**, 3482–3485; (e) V. Pagar and T. V. RajanBabu, *Science*, 2018, **361**, 68–72. For reviews: (f) T. Bach and J. P. Hehn, *Angew. Chem., Int. Ed.*, 2011, **50**, 1000–1045; (g) Y. Xu, M. L. Conner and M. K. Brown, *Angew. Chem., Int. Ed.*, 2015, **54**, 11918–11928.
- (a) W. R. Gutekunst and P. S. Baran, *J. Am. Chem. Soc.*, 2011, **133**, 19076–19079; (b) W. R. Gutekunst, R. Gianatassio and P. S. Baran, *Angew. Chem., Int. Ed.*, 2012, **51**, 7507–7510; (c) R. Parella, B. Gopalakrishnan and S. A. Babu, *J. Org. Chem.*, 2013, **78**, 11911–11934; (d) W. R. Gutekunst and P. S. Baran, *J. Org. Chem.*, 2014, **79**, 2430–2452; (e) K.-J. Xiao, D. W. Lin, M. Miura, R.-Y. Zhu, W. Gong, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 8138–8142; (f) T. Chen, L. M. Barton, Y. Lin, J. Tsien, D. Kossler, I. Bastida, S. Asai, C. Bi, J. S. Chen, M. Shan, H. Fang, F. G. Fang, H.-W. Choi, L. Hawkins, T. Qin and P. S. Baran, *Nature*, 2018, **560**, 350–354; (g) Z. Zhuang, C.-B. Yu, G. Chen, Q.-F. Wu, Y. Hsiao, C. L. Joe, J. X. Qiao, M. A. Poss and J.-Q. Yu, *J. Am. Chem. Soc.*, 2018, **140**, 10363–10367; (h) H. Shi, A. N. Herron, Y. Shao, Q. Shao and J.-Q. Yu, *Nature*, 2018, **558**, 581–585; (i) H. Park, P. Verma, K. Hong and J.-Q. Yu, *Nat. Chem.*, 2018, **10**, 755–762; (j) Q.-F. Wu, X.-B. Wang, P.-X. Shen and J.-Q. Yu, *ACS Catal.*, 2018, **8**, 2577–2581.
- (a) L. M. Chapman, J. C. Beck, L. Wu and S. E. Reisman, *J. Am. Chem. Soc.*, 2016, **138**, 9803–9806; (b) L. M. Chapman, J. C. Beck, C. R. Lackner, L. Wu and S. E. Reisman, *J. Org. Chem.*, 2018, **83**, 6066–6085.
- (a) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154–13155; (b) D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2010, **132**, 3965–3972; (c) K.-J. Xiao, D. W. Lin, M. Miura, R.-Y. Zhu, W. Gong, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 8138–8142. For a review: (d) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754–8786.
- (a) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle and D. W. C. MacMillan, *Science*, 2014, **345**, 437–440; (b) C. P. Johnston, R. T. Smith, S. Allmendinger and D. W. C. MacMillan, *Nature*, 2016, **536**, 322–325; (c) K. M. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. G. Ackerman and D. J. Weix, *J. Am. Chem. Soc.*, 2016, **138**, 5016–5019; (d) J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C.-M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2016, **138**, 2174–2177; (e) N. Suzuki, J. L. Hofstra, K. E. Poremba and S. E. Reisman, *Org. Lett.*, 2017, **19**, 2150–2153; (f) J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D.-H. Bao, F.-L. Wei, T. Zhou, M. D. Eastgate and P. S. Baran, *Nature*, 2017, **545**, 213–218; (g) L. Huang, A. M. Olivares and D. J. Weix, *Angew. Chem., Int. Ed.*, 2017, **56**, 11901–11905; (h) A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers and V. K. Aggarwal, *Science*, 2017, **357**, 283–286; (i) W.-M. Cheng, R. Shang, M.-C. Fu and Y. Fu, *Chem.-Eur. J.*, 2017, **23**, 2537–2541. Reviews: (j) N. Rodríguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030–5048; (k) S. Murarka, *Adv. Synth. Catal.*, 2018, **360**, 1735–1753.
- Use of 1.0 equivalent of aryl iodide or lowering the catalyst loading to 7.5 mol% reduced the yield for most substrates by approximately 30%.
- Unfortunately, our efforts to derivatize the 8-aminoquinolinamide without epimerization to the *trans*-cyclobutane proved unfruitful.
- J. E. Steves and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 15742–15745.
- A. C. Wotal and D. J. Weix, *Org. Lett.*, 2012, **14**, 1476–1479.
- Several direct decarboxylative coupling reactions using [Ir]/[Ni] catalyst systems performed poorly on this substrate. For example, cross-coupling of **10** with 3-phenyl-1-bromopropane under [Ir]/[Ni] (see ref. 8b) resulted in formation of the corresponding ester.
- Prior syntheses: (a) T. Hirokawa, T. Nagasawa and S. Kuwahara, *Tetrahedron Lett.*, 2012, **53**, 705–706; (b) T. Hirokawa and S. Kuwahara, *Tetrahedron*, 2012, **68**, 4581–4587; (c) B. Ranieri, C. Obradors, M. Mato and A. M. Echavarren, *Org. Lett.*, 2016, **18**, 1614–1617; (d) C. García-Morales, B. Ranieri, I. Escofet, L. López-Suarez,



- C. Obradors, A. I. Konovalov and A. M. Echavarren, *J. Am. Chem. Soc.*, 2017, **139**, 13628–13631.
- 15 Under the conditions reported in Table 2, significant amounts of a bis-arylated product (by HRMS) was formed. Use of 2-iodofuran instead for **23** resulted in lower yields.
- 16 Adapted from: L. Chu, C. Ohta, Z. Zuo and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2014, **136**, 10886–10889.
- 17 S. P. Annangudi, M. Sun and R. G. Salomon, *Synlett*, 2005, 1468–1470.
- 18 (a) M. T. R. R. Steinbach, J. Westermann, R. Peter and B. Wenderoth, *Chem. Ber.*, 1985, **118**, 1441–1454; (b) W. H. Miles, D. G. Duca, J. T. Freedman, E. O. Goodzeit, K. B. Hamman, S. C. A. P. De and B. R. Selfridge, *Heterocycl. Commun.*, 2011, **13**, 195–198; (c) A. Zúñiga, G. Pazos, P. Besada and Y. Fall, *Tetrahedron Lett.*, 2012, **53**, 4293–4295.
- 19 M. T. Reetz, J. Westermann and S.-H. Kyung, *Chem. Ber.*, 1985, **118**, 1050–1057.

