Published in final edited form as:

Angew Chem Int Ed Engl. 2012 July 23; 51(30): 7507–7510. doi:10.1002/anie.201203897.

Sequential C(sp³)-H arylation and olefination: total synthesis of the proposed structure of pipericyclobutanamide A

Will R. Gutekunst, Ryan Gianatassio, and Prof. Dr. Phil S. Baran

Department of Chemistry, The Scripps Research Institute 10650 North Torrey Pines Road, La Jolla, CA, 92037 (USA) Fax: (+1) 858-784-7375

Phil S. Baran: pbaran@scripps.edu

Abstract

Hip to be square—A strategy for assembling tetrasubstituted cyclobutanes is reported in the context of a short, protecting-group-free synthesis of the proposed structure of pipericyclobutanamide A. The route features sequential C–H functionalizations on an unactivated cyclobutane wherein C–C bonds to aryl and styrenyl groups are made one-by-one in a stereocontrolled fashion.

Keywords

cyclobutanes; C–H functionalization; pipericyclobutanamide

Our laboratory recently reported the synthesis of the pseudodimeric cyclobutane natural products piperarborenine B (**1**, Figure 1A) and piperarborenine D (proposed structure, **2**) through a sequential cyclobutane C–H arylation strategy.^[1,2] This led to both the concise preparation of these molecules (6–7 steps) and the structural reassignment of piperarborenine D (revised structure, **3**). While the piperarborenines are the simplest examples of heterodimeric cyclobutane natural products isolated from pepper plants, a number of other heterodimers have been isolated, which all arise from a formal [2+2] cycloaddition of piperine-like monomers (**4**) with varying oxidation states and chain lengths.^[3] Looking to extend our C–H functionalization strategy to more complex members of the family, our attention turned to the pipericyclobutanamides (**5** and **6**).

The pipericyclobutanamides were first isolated by Fujiwara and coworkers in 2001 from the fruits of the black pepper plant, *Piper nigrum*, though no biological activity was reported at that time.^[3a] In 2006, Tezuka and coworkers reisolated pipericyclobutanamide A (**5**) and demonstrated a selective inhibition of cytochrome P450 2D6 (CYP2D6).^[3c] These heterodimers represent a greater synthetic challenge than the piperarborenines (**1,3**) due to the presence of four different substituents on the cyclobutane ring. Both of these natural products contain an unusual *cis* unsaturated amide, and pipericyclobutanamide A (**5**) and B (**6**) contain styrene and styryl diene motifs, respectively. Viewing these molecules as an opportunity to develop cyclobutane C–H olefination chemistry, a synthetic strategy was devised and the retrosynthetic analysis of pipericyclobutanamide A (**5**) is shown in Figure 1B. First, the *cis*-alkene is transformed into an aldehyde through a stereocontrolled olefination reaction. The aldehyde could then be deconstructed to a directing group (DG) and the amide into a methyl ester using standard functional group manipulations to provide

Correspondence to: Phil S. Baran, pbaran@scripps.edu.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author. ((Please delete if not appropriate))

intermediate **7**. Applying the strategy developed for the piperarborenines, this intermediate could be prepared through a series of epimerizations and sp^3 C–H functionalizations on a desymmetrized cyclobutane dicarboxylate **8**.

The direct olefination of sp^2 C–H bonds has been known since the seminal work of Fujiwara and Moritani in the late 1960's,^[4] but few examples exist for the direct olefination of unactivated sp^3 C–H bonds.^[5] During a study towards the teleocidin natural products, Sames coupled an unactivated methyl group with a vinyl boronic acid, though the sequence proceeded through a discretely isolated palladacycle.^[5e] The first catalytic example was reported in 2010 by Yu and coworkers.^[5a] A highly electron-deficient anilide directing group was employed to couple acrylate derivatives directly to unactivated methyl and cyclopropyl C–H bonds. Chen and coworkers later reported the coupling of cyclic vinyl iodides with methylene C–H bonds using Daugulis' picolinamide directing group under palladium catalysis.^[5d] Encouraged by this result in particular, a styrenyl iodide was chosen as the first coupling partner to examine for the synthesis of pipericyclobutanamide **A** (**5**).^[6]

Investigations started with the preparation of the requisite cyclobutane starting material **12** (Scheme 1). Applying the methodology developed previously for the piperarborenine natural products, methyl coumalate (**9**) underwent photochemical 4π electrocycloization at reduced temperature to give photopyrone **10**.^[7] This unstable intermediate was immediately hydrogenated and coupled to 8-aminoquinoline^[8] in a single operation to give the desired C–H olefination precursor (**12**) in 54% overall yield. The olefination reaction was initially studied with (2-iodovinyl)benzene as a model coupling partner. The use of conditions originally developed for monoarylation (hexafluoroisopropanol (HFIP) as solvent and pivalic acid) resulted in low conversion and significant amounts of decomposition. Switching the solvent to toluene improved the reaction considerably to give bis-olefinated cyclobutane **13** as the major product in 50% isolated yield. This is in contrast to our previous work on the piperarborenines in which an epimerization event was required to allow for an efficient second C–H functionalization on the cyclobutane ring. The reason for this direct bis-olefination is unclear, but it may simply be that the vinyl iodide is smaller than the aryl iodide, leading to a more facile second reaction. Furthermore, **13** is an all-*cis*-cyclobutane that is quite strained and, to our knowledge, there are no other general methods for the controlled construction of this stereochemical array on a cyclobutane.

Given the modularity of this sequential C–H functionalization strategy, a monoarylation reaction could take place, followed by an olefination reaction to reach the end goal. When the standard monoarylation conditions were applied to reaction of cyclobutane **12** with 1-iodo-3,4-methylenedioxybenzene, poor conversion was observed due to methylenedioxy ring (3,4-dimethoxyiodobenzene as a coupling partner performed well). Pivalic acid proved to be an effective additive, and when the reaction was performed in t -BuOH at high concentration, an acceptable monoarylation yield was obtained (54%, 1.00g scale). Due to the facile double olefination observed in the preparation of **13**, monoarylated **14** was directly subjected to the C–H olefination reaction with styrenyl iodide **15**. Optimizing the reaction was straightforward, employing catalytic $Pd(OAc)_2$ in the presence of 1.5 equivalents of $AgOAc$ with toluene as the solvent gave all-*cis*-cyclobutane **16** in 59% yield (480 mg scale). Pivalic acid as an additive retarded the reaction rate, and protic solvents such as t -BuOH or HFIP were inferior, giving low conversion or substantial decomposition, respectively.

With the sequential functionalization product (**16**) in hand, the relative stereochemistry needed to be altered to the all-*trans* configuration found in the natural product. This was anticipated to be a facile process given the strained nature of the all-*cis* stereochemistry and the thermodynamically downhill path to the desired all-*trans* product. Experimentally, this was verified through the use of two equivalents of sodium methoxide with C-1

epimerization occurring rapidly at room temperature (< 1 min). Upon warming the reaction mixture to 45 °C, the methyl ester (C-3) epimerizes over two hours and fully hydrolyzes after the addition of aqueous sodium hydroxide to give acid **18**. Without further purification, **18** was treated with excess DIBAL to transform the aminoquinoline directing group directly into an aldehyde. By employing the free carboxylic acid in this reaction, the correct oxidation state found in the natural product is maintained with the carboxylate anion acting as an *innate* protecting group.^[9] Additionally, the direct reduction of secondary amides with DIBAL has limited precedent, and the success of this reaction is likely the result of the chelating nature of the aminoquinoline motif.^[10] Furthermore, this presents a new method for the cleavage of this amide directing group that avoids the extremes of pH and heat, expanding the synthetic utility of the Daugulis methodology if found to be general. Moving forward with the crude reaction product **19**, piperidine was used as both a base and a coupling partner in the reaction with T3P® (propylphosphonic anhydride) to provide amide **20** in 40–45% isolated yield over 3 steps (114 – 386 mg scale).

To complete the synthesis of pipericyclobutanamide A (**5**), only an olefination reaction remained. This was accomplished through the use of Ando's methodology for *cis*-selective unsaturated amide synthesis.^[11] Treatment of aldehyde **20** with the Ando phosphonate (**21**) in the presence of *t*BuOK resulted in a *ca.* 5:1 *cis:trans* mixture of easily separable olefin isomers, giving the desired pipericyclobutanamide A (**5**) in 80% isolated yield (100 mg scale). Unfortunately, the ¹H and ¹³C NMR data did not match the spectrum reported for the natural product.^[12]

The concise synthesis of the proposed structure of pipericyclobutanamide A (**5**) further demonstrates the power of C–H functionalization logic in synthesis to provide substantial amounts of complex cyclobutanes (7 steps, 5 chromatographic purifications, 5% overall yield, >100 mg prepared). The sequence features mostly skeleton-forming transforms, is protecting-group-free,^[13] and has only one concession step (DIBAL reduction) leading to an ideality of 85%.^[14] Salient features of the synthesis include: (1) the first example of C–H olefination on an unactivated cyclobutane ring; (2) stereocontrolled access to highly strained all-*cis* cyclobutanes; (3) direct conversion of aminoquinoline amides directly to aldehydes; and (4) the use of a carboxylate anion as an “innate protecting group” in an amide reduction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to Dane Holte for technical assistance. Financial support for this work was provided by the NIH/NIGMS (GM-073949) and the NSF for a predoctoral fellowship to W.R.G.

References

1. Gutekunst WR, Baran PS. J Am Chem Soc. 2011; 133:19076–19079. [PubMed: 22066860] for reviews on C–H functionalization in synthesis: Taber DF, Stiriba SE. Chem Eur J. 1998; 4:990–992. Godula K, Sames D. Science. 2006; 312:67–72. [PubMed: 16601184] Davies HM, Manning JR. Nature. 2008; 451:417–424. [PubMed: 18216847] Ishihara Y, Baran PS. Synlett. 2010; 12:1733–1745. Gutekunst WR, Baran PS. Chem Soc Rev. 2011; 40:1976–1991. [PubMed: 21298176] McMurray L, O'Hara F, Gaunt MJ. Chem Soc Rev. 2011; 40:1885–1898. [PubMed: 21390391] Brückl T, Baxter RD, Ishihara Y, Baran PS. Acc Chem Res. 2011 10.1021/ar200194b
2. a) Lee FP, Chen YC, Chen JJ, Tsai IL, Chen IS. Helv Chim Acta. 2004; 87:463–468. b) Tsai IL, Lee FP, Wu CC, Duh CY, Ishikawa T, Chen JJ, Chen YC, Seki H, Chen IS. Planta Med. 2005; 71:535–542. [PubMed: 15971125]

3. a) Fujiwara Y, Naithou K, Miyazaki T, Hashimoto K, Mori K, Yamamoto Y. *Tetrahedron Lett.* 2001; 42:2497–2499. b) Wei K, Li W, Koike K, Chen Y, Nikaido T. *J Org Chem.* 2005; 70:1164–1176. [PubMed: 15704948] c) Tsukamoto S, Tomise K, Miyakawa K, Cha BC, Abe T, Hamada T, Hirota H, Ohta T. *Bioorg Med Chem.* 2002; 10:2981–2985. [PubMed: 12110320] d) Subehan T, Usia S, Kadota Y, Tezuka. *Planta Med.* 2006; 72:527–532. [PubMed: 16808005] e) Sharma RL, Kumari M, Kumar N, Prabhakar A. *Fitoterapia.* 1999; 70:144–147. f) Matsuda H, Ninomiya K, Morikawa T, Yasuda D, Yamaguchi I, Yoshikawa M. *Bioorg Med Chem.* 2009; 17:7313–7323. [PubMed: 19775895]
4. a) Moritani I, Fujiwara Y. *Tetrahedron Lett.* 1967; 8:1119–1122. b) Jia C, Kitamura T, Fujiwara Y. *Acc Chem Res.* 2001; 34:633–639. [PubMed: 11513570]
5. a) Wasa M, Engle KM, Yu JQ. *J Am Chem Soc.* 2010; 132:3680–3681. [PubMed: 20187642] b) Wasa M, Engle KM, Lin DW, Yoo EJ, Yu JQ. *J Am Chem Soc.* 2011; 133:19598–19601. [PubMed: 22059375] c) Stowers KJ, Fortner KC, Sanford MS. *J Am Chem Soc.* 2011; 133:6541–6544. [PubMed: 21476513] d) He G, Chen G. *Angew Chem Int Ed.* 2012; 50:5192–5196. e) Dangel BD, Godula K, Youn SW, Sezen B, Sames D. *J Am Chem Soc.* 2002; 124:11856–11857. [PubMed: 12358522]
6. Daugulis has successfully coupled a styrenyl iodide to an sp^2 center using the 8-aminoquinoline directing group: Shabashov D, Daugulis O. *J Am Chem Soc.* 2010; 132:3965–3972. [PubMed: 20175511]
7. a) Frébaud F, Luparia M, Oliveira MT, Goddard R, Maulide N. *Angew Chem Int Ed.* 2010; 49:5672–5676. b) Corey EJ, Streith J. *J Am Chem Soc.* 1964; 86:950–951. c) Javaheripour H, Neckers DC. *J Org Chem.* 1977; 42:1844–1850. d) Luparia M, Oliveira MT, Audisio D, Frébaud F, Goddard R, Maulide N. *Angew Chem Int Ed.* 2011; 50:12631–12635.
8. Zaitsev VG, Shabashov D, Daugulis O. *J Am Chem Soc.* 2005; 127:13154–13155. [PubMed: 16173737] b) studies on a model system demonstrated higher reactivity of the 8-aminoquinoline directing group in the olefination chemistry relative to 2-aminothioanisole.
9. This strategy was inspired by Barton's clever use of enolate anions as protecting groups: Barton DHR, Hesse RH, Wilshire C, Pechet MM. *J Chem Soc Perkin.* 1977; 1:1075–1079.
10. Schmitz FU, Tai VW-F, Rai R, Roberts CD, Abadi ADM, Baskaran S, Slobodov I, Maung J, Neitzel ML. Genelabs Technologies, Inc WO. 2009023179. 2009 other methods for the direct reduction of secondary amides to aldehydes: Pelletier G, Bechara WS, Charette AB. *J Am Chem Soc.* 2010; 132:12817–12819. [PubMed: 20735125] Bower S, Kreutzer KA, Buchwald SL. *Angew Chem Int Ed.* 1996; 35:1515–1516. Spletstoser JT, White JM, Tunoori AR, Georg GI. *J Am Chem Soc.* 2007; 129:3408–3419. [PubMed: 17315870]
11. Ando K, Nagaya S, Tarumi Y. *Tetrahedron Lett.* 2009; 50:5689–5691.
12. While this work was in progress, we became aware of the elegant studies of the Tang group whose first and asymmetric synthesis of **5** indicated that the natural product is misassigned and that the real pipericyclobutanamide A is actually the constitutionally isomeric cyclohexene containing natural product chabamide: Liu R, Zhang M, Wyche TP, Winston-McPherson GN, Bugni TS, Tang W. *Angew Chem Int Ed.* 2012 10.1002/anie.201203379
13. Young IS, Baran PS. *Nat Chem.* 2009; 1:193–205. [PubMed: 21378848]
14. Gaich T, Baran PS. *J Org Chem.* 2010; 75:4657–4673. [PubMed: 20540516]

Figure 1.
Selected heterodimeric cyclobutane natural products and retrosynthesis of
pipercyclobutanamide A (5)

Scheme 1.

Total synthesis of the proposed structure of pipericyclobutanamide A (**5**). Reagents and conditions: a) 450-W Hanovia lamp, Pyrex filter, DCM, 15 °C, 96 h; then H₂, Pt/C, 4 h; then 8-aminoquinoline (1.2 equiv), EDC (1.2 equiv), 0 to 23 °C, 3 h, 54%; b) (2-iodovinyl)benzene (3.0 equiv), Pd(OAc)₂ (0.15 equiv), AgOAc (3.0 equiv), PhMe, 80 °C, 12 h, 50%; c) Pd(OAc)₂ (0.15 equiv), Ag₂CO₃ (1.0 equiv), PivOH (1.0 equiv), 1-iodo-3,4-methylenedioxybenzene (2.0 equiv), ^tBuOH, 85 °C, 15 h, 54%; d) **15** (2 equiv), Pd(OAc)₂ (0.15 equiv), AgOAc (1.5 equiv), PhMe, 80 °C, 10 h, 59%; e) NaOMe (2.0 equiv), MeOH:THF (1:4), 45 °C, 2 h, then 1N NaOH, 1 h; f) DIBAL (3.5 equiv), THF, –78 °C, 0.5 h; g) piperidine (3.0 equiv), T3P® (1.5 equiv), DCM, 23 °C, 15 min, 40–45% (3 steps); h) **21** (1.5 equiv), KO^tBu (1.5 equiv), THF, –78 °C to 0 °C, 2 h, 80%. EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, T3P® = propylphosphonic anhydride.